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CONTENTS

	PAGE
Clinical and Pathological Details of Two Cases of Phaeochromocytoma in Childhood. M. J. Robinson and Alan Williams	69
A Study of Serum Bilirubin Levels in Relation to Kernikterus and Prematurity. Thomas C. Meyer	75
The Recognition of Primary Tuberculous Infection of the Mouth. J. Boyes, J. D. T. Jones and F. J. W. Miller	81
Whooping Cough Encephalitis. A. L. Woolf and H. Caplin	87
Hydrops Foetalis Successfully Treated by Exchange Transfusion. Josephine Cook	92
Laryngeal Stenosis with Tracheostomy Treated by Hemi-laryngectomy and Reconstruction of the Laryngeal Orifice. H. S. Sharp	94
Klebsiella pneumoniae (Friedländer's Bacillus) Infections in Infancy. Béla Steiner and Gyula Putnoky	96
Acute Glomerulonephritis in Infancy. T. N. Fison	101
Hydronephrosis in Infancy. A. R. Bearn	110
A Histochemical Study of Pulmonary Hyaline Membrane. F. Duran-Jorda, A. Holzel and W. H. Patterson	113
Radiological Findings in the Lungs of Premature Infants. John Fawcitt	119
Single Polyp of the Large Intestine in Childhood. J. R. Hughes, R. T. Jenkins and D. E. Sturdy	124
Blood Pressure in the Newborn Estimated by the Flush Method. John O. Forfar and Maurice A. Kibel	126
Coexistent Aplastic Anaemia and Coarctation of the Aorta. J. P. Anderson	131
Subcutaneous Emphysema Complicating Asthma. J. R. K. Henry	133
Clinical Aspects of Congenital Tuberculosis. F. P. Hudson	136
Studies in a Case of 'Renal Rickets'. Kenneth Sinclair	140
Exomphalos. A. A. Cunningham	144
Paediatric Societies in the British Isles	152

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CLINICAL AND PATHOLOGICAL DETAILS OF TWO CASES OF PHAEOCHROMOCYTOMA IN CHILDHOOD

BY

M. J. ROBINSON and ALAN WILLIAMS

From the Royal Children's Hospital, Melbourne

(RECEIVED FOR PUBLICATION JANUARY 6, 1956)

Hypertension due to the presence of a tumour of the adrenal medulla was first described by Labbé, Tinel and Doumer in 1922. Four years later such a tumour was successfully removed by Roux (1926). The literature concerning phaeochromocytoma in childhood was recently reviewed by Daeschner, Moyer and Able (1954). They were able to find only 16 recorded cases of active phaeochromocytoma in children under the age of 14 years, to which number they added one further case. Three cases have been recorded since then (Negri and Pugno Vanoni, 1954; Mégevand and Ferrier, 1954; Popper and Theron, 1954).

We record the clinical notes, including diagnosis and operative management, of two children aged 8 and 10 years respectively in each of whom a phaeochromocytoma was discovered and successfully removed. The investigation of hypertension detected on routine physical examination led to the diagnosis and removal of the tumours. This was followed in each case by a reversion of blood pressure to normal levels, and alleviation of symptoms. The nature of the tumours was confirmed by histological studies and hormone assays.

Case Reports

Case 1. A.L., a boy aged 8 years and 7 months was perfectly well until about two years before admission when it was first noticed that he sweated profusely. The sweating was not related particularly to the environmental temperature, but was more pronounced at night. Frontal headaches began six months before admission. These occurred once or twice weekly, usually early in the morning and lasted several hours.

Two months later puffiness and redness of both hands and wrists were noticed. The lower extremities had never shown vasomotor changes. One month before

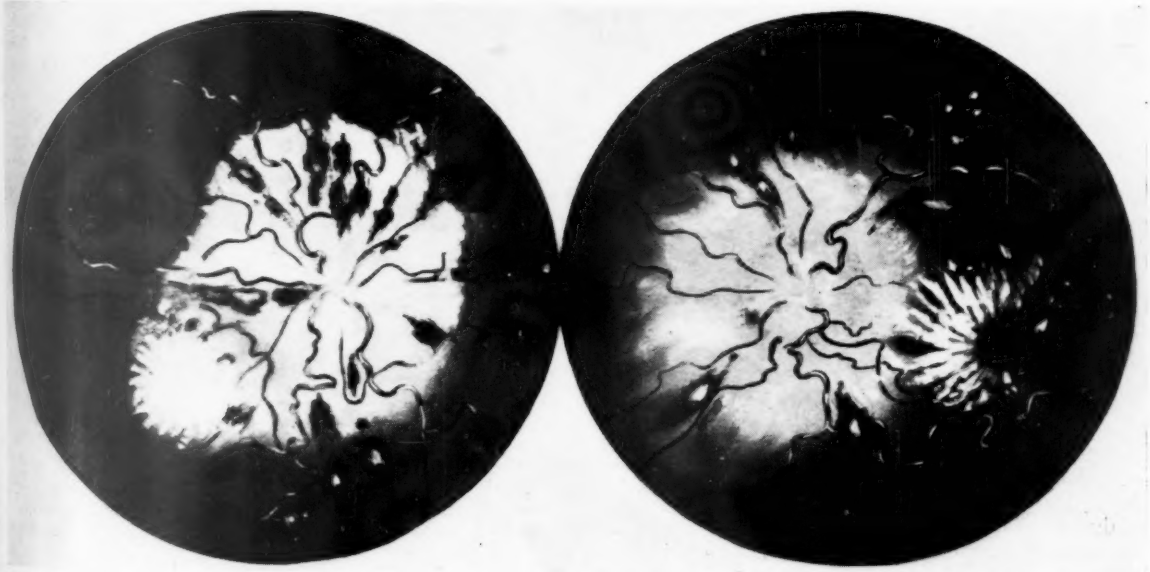

FIG. 1.—Drawing of the ocular fundi in Case 1 showing bilateral papilloedema, flame-shaped haemorrhages, and exudate. There is a well developed macular star in the right ocular fundus.

admission the boy complained of progressive difficulty of vision and of a grey shadow before his eyes. Over the past few weeks he had been excessively thirsty and wanted additional salt with his meals. There had been no urinary symptoms or nocturia.

On examination he was a cooperative, intelligent boy of normal physical development. The heart was slightly enlarged, the impulse being located 3¼ in. from the mid-sternal line. The aortic second sound was accentuated. Both femoral arteries were easily palpable. The blood pressure was 200/160 mm. Hg.

Retinoscopy showed bilateral papilloedema with a large amount of exudate and scattered haemorrhages. There was a well defined macular star in the right fundus. The vessels were tortuous and thickened (Fig. 1).

The only other significant findings on physical examination were swollen red hands and wrists. The skin over the hands was coarse and dry, but pitting on pressure was not possible.

LABORATORY TESTS. Repeated urine tests showed traces of albumin but no sugar. The specific gravity of the urine ranged between 1,010 and 1,025 and microscopy revealed an occasional hyaline cast only. The blood urea was 44 mg. per 100 ml. and urea clearance and concentration tests showed normal function. An intravenous pyelogram was normal.

Radiological examination of the thorax showed very slight cardiac enlargement but the electrocardiogram was normal. The haemoglobin level was 15·5 g. per 100 ml., and leucocytes 12,850 per c.mm. with a normal differential cell count. Wassermann and Kahn tests were negative. The fasting blood sugar was 112 mg. per 100 ml.

Phentolamine Test. An intravenous infusion was set up and approximately one hour later, when the blood pressure was stable, 2·5 mg. of phentolamine ('regitine', Ciba Ltd.) in 10 ml. of saline was injected slowly and

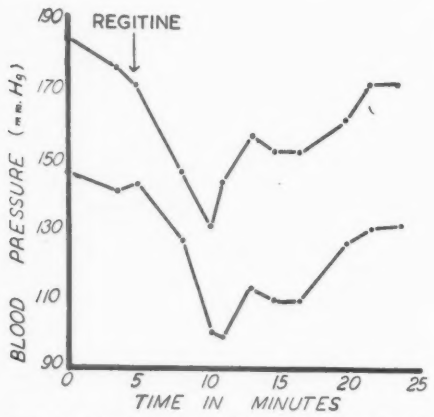

FIG. 2.—Fall in blood pressure (Case 1) following intravenous injection of 'regitine' before removal of the tumour.

produced a fall of approximately 40 mm. Hg in both systolic and diastolic pressures (Fig. 2).

Urine Assay. Confirmation of the diagnosis of phaeochromocytoma was obtained by biological assay of a 24-hour specimen of urine which was found to contain 300 μg. per litre of pressor amine.*

RADIOLOGY. The tumour was demonstrated by combining retroperitoneal air insufflation and angiography. This procedure was performed under general anaesthesia and the blood pressure controlled by phentolamine. This investigation demonstrated an enlarged right adrenal shadow. On the left side no adrenal shadow was visible.

From the time the diagnosis was considered until operation was performed, the boy was maintained on oral phentolamine, 20 mg. six-hourly. This enabled a constant blood pressure of 160/120 mm. Hg to be maintained, and relieved much of his sweating, headache and giddiness. However, he developed a tolerance to oral phentolamine and the dosage had to be increased to 30 mg. four-hourly.

For three days before operation he was given cortisone, 20 mg. orally, each day.

OPERATION. At operation under thiopentone, tubocurarine chloride, nitrous oxide and oxygen, the right adrenal gland was exposed via a right transthoracic extraperitoneal approach and a tumour palpated in its substance. This was enucleated following ligation and division of its blood vessels.

Manipulation during excision of a phaeochromocytoma results in large quantities of adrenaline and noradrenaline being liberated into the circulation with the consequent development of sudden and profound hypertension. Removal of the tumour is usually followed by sudden circulatory failure presumably due to deprivation of the large quantities of vasoconstrictor hormone to which the patient has been accustomed. In this patient during manipulation of the tumour, a total of 4·75 mg. of phentolamine was intermittently injected, and, following the initial level of 190/160 mm. Hg, at no stage did the blood pressure exceed 240/170 mm. Hg. When the

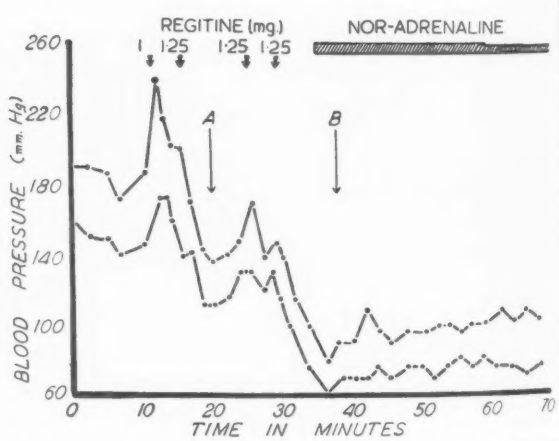

FIG. 3.—Chart illustrating control of blood pressure (Case 1) by the use of 'regitine' and nor-adrenaline during operative removal of tumour. (A denotes when tumour was palpated and B when tumour was removed.)

* Throughout this paper the pressor amine content is expressed in terms of nor-adrenaline.

vessels to the tumour were clamped the blood pressure rapidly fell to 80/60 mm. Hg and the infusion of intravenous nor-adrenaline was immediately begun, the rate of flow being adjusted to maintain a systolic pressure greater than 100 mm. Hg. This required between 6 and 10 μg. of nor-adrenaline per minute. By the end of the operation, the blood pressure was constant at 115/80 mm. Hg and the nor-adrenaline was stopped. The variations of the blood pressure and measures to control them are illustrated in Fig. 3.

The post-operative period was uneventful. Headaches and sweating completely disappeared and his vision had greatly improved. In the few weeks before his discharge from hospital the systolic pressure fluctuated between 125 and 135 mm. Hg and the diastolic between 84 and 95 mm. Hg. The blood urea following operation was 24 mg. per 100 ml. A 24-hour specimen of urine contained 40 μg. per litre of pressor amine, a normal value. Three months after operation the papilloedema and haemorrhages had almost completely resolved, and the exudates were much reduced (Fig. 4).

PATHOLOGY. The tumour, together with its surrounding rim of adrenal cortex, weighed 22 g. Transection revealed a solid pink tissue of uniform appearance throughout. Within 15 minutes of its surgical removal portions of tissue were placed in formalin, Regaud's fluid, and in osmic acid vapour.

Histological preparations showed that the tumour had a dense fibrous capsule, which separated it from adrenal cortical tissue. Traversing the tumour were numerous fibrous septa, the spaces between which were occupied by groups of cells with indistinct outlines (Fig. 5). The majority of cells consisted of nuclei surrounded by a varying amount of cytoplasm and by clear spaces. The nuclei varied in size, many being large and containing prominent nucleoli. Multinucleated cells containing two to four nuclei were present but not numerous. No differentiated nervous tissue or ganglion cells were seen in numerous sections prepared. The tumour was extremely vascular, many thin-walled vessels being present in fibrous septa and amongst the cells so that they often formed the walls of the vessel.

The formalin in which tissue was fixed became pale brown within 24 hours. Material fixed in Regaud's fluid rapidly became dark brown and in sections stained with haematoxylin and eosin numerous dark brown granules were seen. These granules were, however, best demonstrated by Sevki's modification of Schmorl's Giemsa stain (Pearse, 1953) after which they became bright green (Fig. 6). Their osmiophilic nature was seen in material fixed by osmic acid, and from which fats were extracted. Fat globules within tumour cells was demonstrated by this method and also by frozen sections from formalin stained with Sudan III. The high fat content did not appear to account entirely for the vacuolated appearance of the cells seen in sections of paraffin-embedded tissue.

The pressor amine content of the tumour was 1,370 μg. per g. of tissue.

Case 2. G.B., a boy aged 10 years and 9 months, was well until about eight months before admission to hospital when his parents noticed increasing pallor. About this time he complained of headaches. These occurred about once a week, usually situated over the vertex and lasted from one to eight hours. Occasionally the headaches were associated with vomiting. Sweating was noticed only occasionally and then usually at night.

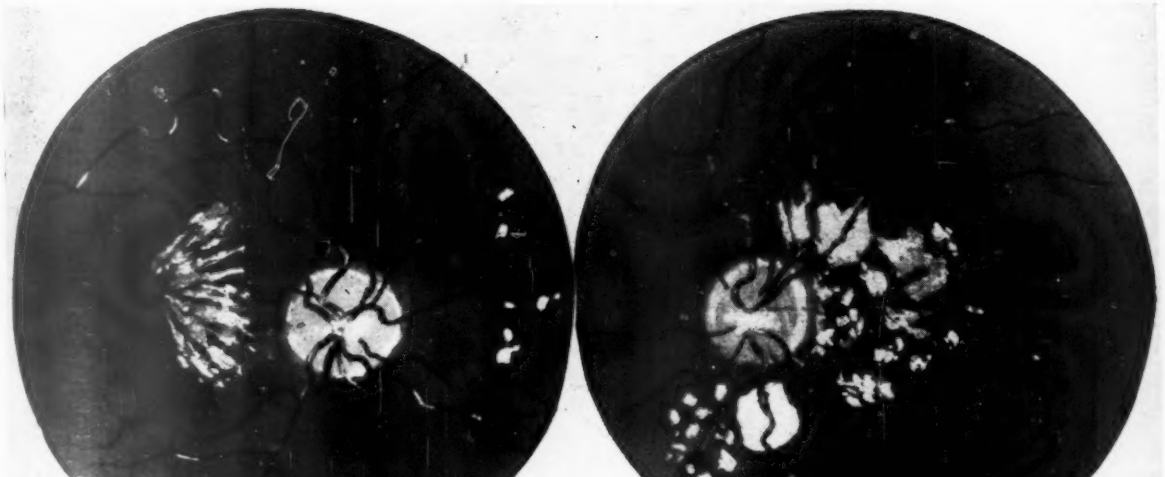

FIG. 4.—Drawing of the ocular fundi in Case 1 three months after removal of the phaeochromocytoma. Papilloedema and haemorrhages have disappeared. The amount of exudate is greatly reduced.

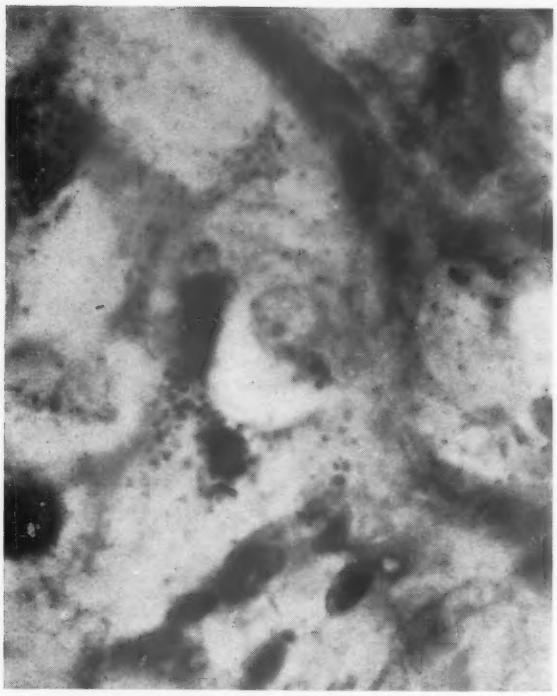

FIG. 5.—Photomicrograph of tumour (Case 1) showing groups of poorly defined cells between connective tissue septa. (Haematoxylin and eosin × 100.)

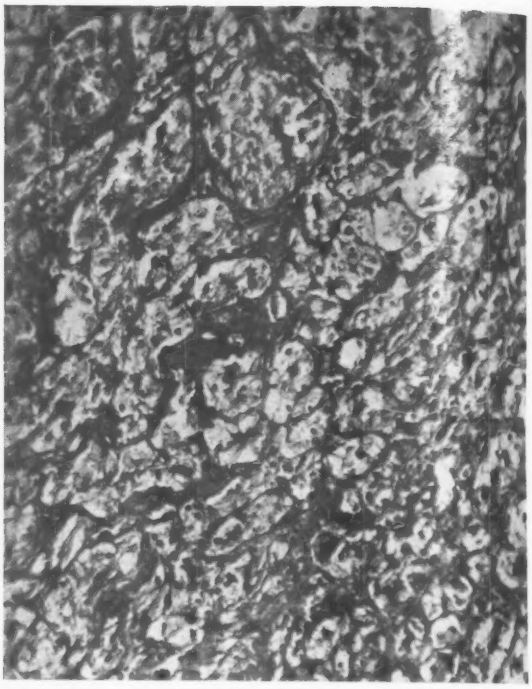

FIG. 6.—Photomicrograph showing granules within cells of phaeochromocytoma (Case 1). (Schmorl's modification of Giemsa stain × 980.)

At no stage had he complained of visual disturbances, or symptoms referable to the renal system.

His private doctor found hypertension and a cardiac bruit and referred the boy to hospital for investigation.

On examination, the abnormal physical findings were confined to the cardiovascular system. The heart was enlarged, the impulse being located 4 in. from the midsternal line in the fifth left intercostal space. A triple rhythm was audible over the whole of the precordium and a blowing diastolic bruit down the left border of the sternum. The blood pressure was 180/130 mm. Hg. All major arteries of the lower limbs were readily palpable. The ocular fundi were normal.

LABORATORY TESTS. Repeated urine tests showed an occasional trace of albumin but no sugar. Several urine specimens were normal on microscopy. The blood urea was 28 mg. per 100 ml. A concentration-dilution test, a urea clearance test and an intravenous pyelogram gave normal results. Radiological examination of the thorax revealed slight cardiac enlargement. An electrocardiogram showed left axis deviation and slight left ventricular hypertrophy. The haemoglobin was 17·2 g. per 100 ml., leucocytes 10,800 per c.mm. and the differential white cell count normal. Wassermann and Kahn tests were negative, and a glucose tolerance was normal.

Phentolamine Test. After 3 mg. of phentolamine intravenously, the blood pressure fell from 170/100 mm. Hg to 150/50 mm. Hg in eight minutes.

Urine Assay. A 24-hour specimen of urine contained 400 μg. of pressor amine per litre.

RADIOLOGY. Under general anaesthesia, combined retroperitoneal air insufflation and angiography was performed and tomogram films taken. No definite conclusion was reached, but the films suggested the possibility of a left adrenal tumour. During angiography, the blood pressure immediately rose to 230/140 mm. Hg. This promptly returned to the previous level when 1 mg. of phentolamine was injected intravenously.

Throughout this period of investigation, the blood pressure remained fairly constant at 160/110 mm. Hg. Oral phentolamine was not given. Cortisone, 25 mg. daily, was given for three days before operation.

OPERATION. Operation was performed under thiopentone-sodium, gallamine, nitrous oxide and oxygen. The left adrenal gland was exposed via a left transthoracic approach following resection of the tenth left rib. The left adrenal gland was normal, so the incision was enlarged and the abdomen then explored. A mass was found infiltrating the left psoas muscle at the junction of the aorta and the left common iliac artery. This mass was removed with difficulty, there being no suggestion of any plane of cleavage.

The blood pressure was controlled in a similar manner to that in Case 1. Blood pressure readings were taken at least every two minutes (Fig. 7).

The post-operative course was complicated by a left lower lobe pneumonia which responded to chemo-

therapy. Following operation the blood pressure rose again to 160/110 mm. Hg, but just before discharge from hospital was 140/100 mm. Hg. In addition the boy had lost his headaches and was much improved. Urinary nor-adrenaline assay before discharge gave a normal value (16 μg. per litre).

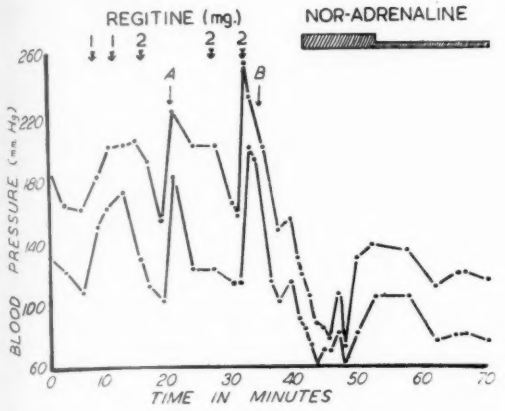

FIG. 7.—Chart illustrating the control of blood pressure (Case 2) by the use of 'regitine' and nor-adrenaline during operative removal of the tumour. (A denotes when tumour was palpated and B when tumour was removed.)

PATHOLOGY. The tumour (weight 16 g.) was lobulated, of a uniform red-brown throughout and possessed a fibrous capsule which was incomplete in one area. Portions of tissue were fixed in a similar manner to the preceding case. In histological preparations a varied appearance was seen in different areas of the tumour. The major part presented an appearance similar to that of Case 1, namely, groups of ill-defined cells within fibrous tissue septa. Granules with staining reactions similar to the preceding case were present in these cells, as were the large irregular clear spaces which contributed largely to the difficulty in distinguishing cell boundaries. In a few areas clumps of smaller cells, with darkly staining nuclei and scanty non-vacuolated eosinophilic cytoplasm, were present. These were often arranged in palisade fashion and resembled nerve fibres, of which several well formed examples were present with the tumour. No ganglion cells were seen. No mitotic figures could be detected and there was no extension beyond the fibrous capsule.

The histological diagnosis was phaeochromocytoma. The pressor amine content of the tumour was 740 μg. per g.

Discussion

When seeking the cause of hypertension in a child, after excluding renal disease and coarctation of the aorta, it is logical to consider a phaeochromocytoma. Essential hypertension and pink disease remain diagnoses of exclusion.

Clinical features associated with the presence of a phaeochromocytoma are due to the secretion of adrenaline and nor-adrenaline by the tumour cells. Variations in the clinical signs and symptoms will vary with the relative amounts of these substances secreted. Adrenaline is responsible for changes in metabolism but the absence of hyperglycaemia and glycosuria in the above cases supports Cahill's (1948) contention that these changes are not frequently found in children with phaeochromocytomas. The secretion of nor-adrenaline is responsible for the hypertension with which these children present. From recorded cases, and our two, the hypertension in such children appears to be constant rather than paroxysmal. Although the hypertension in Case 1 had reached the malignant phase, removal of the tumour still resulted in reversion of all signs and symptoms.

The use of phentolamine appears to be safe and affords valuable evidence of the presence of a phaeochromocytoma. Further and conclusive evidence is afforded by analysis of urine for catechol derivatives. This is done by biological assay and, although time consuming, is warranted in such cases. Pre-operative localization of the tumour may be possible as is demonstrated in Case 1 above. Successful localization of adrenal tumours by presacral air injection has been recorded on many occasions. It appears, however, impossible to localize the extra-adrenal phaeochromocytoma pre-operatively and from the recorded cases it is apparent that a high proportion of such tumours in children are situated in sites other than the adrenals. Thus, including our two cases, in six of the 21 children tumours of extra-adrenal chromaffin tissue have been responsible wholly or partly for the hypertension and accompanying symptoms. This differs from the situation in adults where the literature suggests 10%-15% of phaeochromocytomas are extra-adrenal (Goldenberg, Snyder and Aranow, 1947; Brines and Jennings, 1948). These tumours were in the retroperitoneal tissue near the adrenals, or intimately associated with the abdominal aorta and vena cava, situations in which chromaffin tissue may normally be found in the foetus or infant (Coupland, 1952; Kohn, quoted by Goldenberg *et al.*, 1947).

Multiple phaeochromocytomas are rare in adults, but in six of these 21 children more than one tumour was present. In one hypertensive child recorded by Hubble (1951) four phaeochromocytomas were found at necropsy. The failure of the blood pressure to return to normal after removal of a phaeochromocytoma necessitated further exploratory surgery in a child reported by Goldenberg *et al.* (1947). The symptoms subsided after removal of a second chromaffin tumour. The pre-operative use of phentolamine, together with the prevention of the post-operative fall in blood pressure by nor-

adrenaline, appears to afford a degree of safety to these exploratory and sometimes repeated operations.

The macroscopic and histological appearance of the tumours removed in our cases conform with previous descriptions. Other authors have emphasized the variable macroscopic appearance, the indistinct outlines of cells grouped within their fibrous septa, and the staining reactions of granules within these cells in tissues which have been fixed rapidly after removal from the body. These granules were not demonstrated in all cells and in those cells which did contain granules their numbers varied. The staining reactions of the granules as recorded in Case 1, and which were similar in Case 2, are stated by Pearse (1953) to be due to oxidation of adrenaline precursor substances. As other cytoplasmic constituents may be oxidized with similar colour changes these reactions cannot be regarded as chemically specific for adrenaline, although their presence is usually regarded as characteristic of chromaffin tissue.

Malignant chromaffin tumours are rare and Willis (1953) doubts the accuracy of diagnosis of many tumours recorded as such. McGavack, Benjamin, Speer and Klotz (1942) present evidence of a malignant tumour of the adrenal medulla in a woman who died with numerous metastatic deposits. They accept seven other recorded cases as fulfilling the criteria for diagnosis of a malignant phaeochromocytoma. No such case has been recorded in childhood if, as suggested by these authors, the metastatic spread of tumours with a positive chromaffin reaction is used as the criterion of malignancy.

Summary

The clinical notes of two children with hypertension due to a phaeochromocytoma are reported. The main symptoms were severe sweating and headaches.

Remission of the hypertension and accompanying symptoms followed successful surgical removal of the tumours.

The tumours had the histological structure of phaeochromocytomas and biological assay of portions of both revealed a high nor-adrenaline content.

The value of phentolamine ('regitine') in the diagnosis of a phaeochromocytoma, and in controlling hypertension during the removal of such a tumour is illustrated.

The estimations of nor-adrenaline in urine and in tumour tissue were performed at the Baker Research Institute, Alfred Hospital, Melbourne. We express our gratitude to Dr. A. J. Barnett and Dr. G. A. Bentley of this Institute. For permission to record these cases we would like to thank Dr. R. Southby, Dr. S. W. Williams (physicians), Mr. J. G. Whitaker, Mr. R. N. Howard (surgeons), and Dr. M. McClelland (anaesthetist), who, as members of the senior medical staff of the Royal Children's Hospital, were responsible for the care of these children.

Addendum

Since the preparation of this paper the use of phentolamine in the diagnosis and management of phaeochromocytoma has been discussed by Helps *et al.* (*Lancet*, **2**, 267, 1955).

In the same issue of this journal Richardson *et al.* record the reversal of malignant hypertension due to ectopic phaeochromocytoma, and Davis *et al.* describe a malignant phaeochromocytoma with functioning metastases.

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A STUDY OF SERUM BILIRUBIN LEVELS IN RELATION TO KERNIKTERUS AND PREMATURITY

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 30, 1955)

The staining of the basal ganglia in various conditions not associated with iso-immunization has aroused much interest in recent years. With the introduction of replacement transfusion in the treatment of haemolytic disease, kernikterus due to this disease has become a comparative rarity.

Kernikterus has been described associated with acholuric family jaundice, idiopathic familial hyperbilirubinaemia, and in 1950 two groups of workers, Aidin, Corner and Tovey in Great Britain and Zuelzer and Mudgett in America, independently drew attention to the fact that kernikterus was sometimes associated with prematurity only.

The clinical picture of the premature infant who becomes jaundiced on the third or fourth day of life and by the sixth day exhibits profound jaundice, disinclination to feed, head retraction, changes in muscle tone and cyanosis, and in most cases dies on the sixth or seventh day have been described by Aidin *et al.* (1950), and more recently by Crosse, Meyer and Gerrard (1955).

The post-mortem appearances of kernikterus have aroused much speculation as to the metabolism of the breakdown products of haemoglobin and the pathogenesis of the disease. It has been suggested that bilirubin is the sole cause of the damage to the basal nuclei (Pickles, 1949; Küster and Krings, 1950) whilst other workers have claimed that it is due to some abnormal pigment such as mesobilifuchsin which arises from an underlying metabolic disorder (Schmorl, 1904; Bevis, 1953). The suggestions have been made too that the primary lesion may be asphyxial with a secondary bilirubin invasion (Govan and Scott, 1953; Aidin *et al.*, 1950) or the combination of hyperbilirubinaemia and hypoglycaemia (Gerrard, 1952).

Claireaux, Cole and Lathe (1953) produce convincing evidence that whatever else has occurred the pigment in the brains of these infants at necropsy is bilirubin. Whether the bilirubin is toxic or not, it does appear to be the common factor of all these theories.

Day (1954) has given an indication of the possible mode of action of bilirubin by showing experimentally that oxygen uptake of brain tissue from decapitated rats was depressed by 25% when saturated with bilirubin in concentrations of 20 mg. %.

Waters and Britton (1955) have recently produced staining of the brain in newborn rats by intraperitoneal injection of bilirubin, thus confirming the work of Frohlich and Mirsky (1942). An interesting observation of these latter workers has been their inability to produce staining in animals of over 10 days old.

There is circumstantial evidence which supports the view that bilirubin crosses from the circulation into the cerebral tissue with comparative ease in the newborn (Dereymaeker, 1949; Dine, 1954). It has been shown by Mollison and Cutbush (1951) that kernikterus seldom occurs in infants affected by haemolytic disease if the serum bilirubin levels do not rise above 18 to 20 mg. %.

It appears that bilirubin is likely to be the causative factor of kernikterus, whatever the mode of production of the hyperbilirubinaemia.

A search of the literature revealed very little information on the normal serum bilirubin levels in the full-term and premature infant. Davidson, Merritt and Weech (1941), doing daily bilirubin estimations on 94 newborn infants (no mention was made of maturity or weight), produced a normal curve rising to 4·8 mg. on the second day and then falling. They found that there was a very wide deviation of normal, but they correlated their bilirubin levels in the first 10 days of life with those of cord bilirubin levels and stated that the higher the cord bilirubin level the higher the serum level would rise on succeeding days. Other workers have been unable to confirm this. Davidson found also that where the levels rose high they were reached on the fourth day and were about 12·5 mg. per 100 ml.

Obrinsky, Allen and Anderson (1954) concluded from their daily bilirubin estimations on 27 pre-

mature and 12 full-term babies that there was a slightly higher degree of hyperbilirubinaemia in premature babies, but there was considerable overlapping of individual members. They agreed that the maximal level was reached on the fourth day.

More recently, Billing, Cole and Lathe (1954) estimated the plasma bilirubin levels in 49 babies whose weights varied from $2\frac{1}{2}$ to $10\frac{1}{2}$ lb. They divided these into 1 lb. weight groups and showed that the smallest babies reached the highest levels (up to 14 mg. per 100 ml.) on the sixth day, whereas the larger ones rose only to 2·5 mg. and usually on the second day.

McLean, Lucey and Harris (1955) have studied the serum bilirubin levels on 60 premature infants and the relationship of these levels to the degree of kernikterus in those who did not survive. They report the levels reached in the four babies with kernikterus in the absence of iso-immunization as being 22·8 mg., 13·2 mg., 15·2 mg. and 12·6 mg. per 100 ml. respectively. They make the interesting observation that there is a remarkable drop in the serum bilirubin levels immediately preceding death. This has been noted too by Hsia (1954) in the Seventh M. & R. Pediatric Research Conference Report on Haemolytic Disease.

The present investigation was undertaken with four objects in view: (1) To establish the range of serum bilirubin levels in 46 premature babies who did not develop kernikterus and 47 babies over $5\frac{1}{2}$ lb.; (2) to compare these levels with those of babies who developed kernikterus; (3) to ascertain whether there was any correlation between the bilirubin levels on the second day and the appearance of signs of kernikterus on the sixth day; and (4) to ascertain whether there was any correlation between the serum and the C.S.F. levels of bilirubin and the latter's relationship to kernikterus if any.

Material

The investigation passed through various phases.

Phase 1. Forty-eight premature babies, 46 of whom did not develop kernikterus and two who did, and 47 babies over $5\frac{1}{2}$ lb. were admitted to Sorrento Premature Baby Unit or to one of the lying-in wards at Sorrento Maternity Hospital during that phase. Blood samples were collected from these babies on the second, fourth and sixth days.

Phase 2. Because it was noted that the two affected babies in Phase 1 had high serum bilirubin levels on the second day, specimens were taken on the second day only from the next 51 babies admitted to Sorrento Premature Baby Unit. Four of these developed kernikterus.

Parallel Investigation

A further series was running concurrently in another unit. This consisted of 46 babies of whom five were affected. Serum and C.S.F. estimations of bilirubin were done on various days during the first week of life. It was found fairly early in this series that unless clinical jaundice was marked there was no detectable bilirubin in the C.S.F. so the latter part of this phase was restricted to babies showing marked jaundice and is, therefore, largely selected. All babies in Phases 1 and 2 who developed signs of kernikterus were submitted to lumbar puncture and the bilirubin level estimated in the spinal fluid: these babies were added to this series. Eleven babies in all developed kernikterus and were included in this investigation.

Iso-immunization was excluded serologically in all cases developing kernikterus.

Methods

Venous samples of blood were collected by syringe from the femoral vein in all cases and allowed to clot and retract for two to four hours in dry centrifuge tubes at room temperature. The quantity of bilirubin in the serum was estimated by van den Bergh's reaction using a slight modification of the technique of Malloy and Evelyn (1937) in which total bilirubin is determined by treatment with diazotized sulphanilic acid in aqueous methanol solution, without precipitation of the proteins. A measure of the direct bilirubin is obtained by carrying out a parallel determination in which water is used in place of methanol. Because of the difficulty of obtaining pure bilirubin an artificial standard was used, consisting of a solution of methyl red at *p*H 4·63 (King and Coxon, 1950).

Diazo Reagents. A .. 0·1% sulphanilic acid in 0·1 hydrochloric acid
B .. 0·5% sodium nitrate solution
was prepared at monthly intervals and stored in the refrigerator

Immediately before use 0·5 of B was mixed with 10 ml. of A.

Phosphate Buffer. 0·15% anhydrous sodium phosphate (Na_2HPO_4).

Standard Solution. Analar methyl red, 290 mg., is dissolved in 100 ml. of pure glacial acetic acid. (This stock solution keeps indefinitely if stored in a well-stoppered bottle in a cool dark place.)

Serum or plasma, 0·5 ml., was added to 9·5 ml. of phosphate buffer and three tubes were set up as follows:

(1) 'Blank', containing 1 ml. diazo reagent A+ 4 ml. methanol
(2) 'Direct', containing 1 ml. mixed diazo reagent + 4 ml. water
(3) 'Total', containing 1 ml. mixed diazo reagent + 4 ml. methanol.

To each tube 3 ml. of the diluted serum or plasma was added and mixed well. After 30 minutes the colours were measured against the blank, using Ilford filter No. 624. The colour of about 10 ml. of the methyl red standard solution was measured using water as a blank.

$$\frac{\text{Reading of tube 3}}{\text{Reading of standard}} \times 0{\cdot}4 \times 8 \times 20 = \text{mg. total bilirubin per 100 ml. [serum or plasma}$$

The 'direct' bilirubin was calculated similarly, the equation being:

$$\frac{\text{Reading of tube 2}}{\text{Reading of Standard}} \times 0{\cdot}4 \times \frac{8}{3} \times 20 = \text{mg. direct bilirubin per 100 ml. [serum or plasma}$$

The quantity of indirectly reacting bilirubin was obtained by subtraction of the directly reacting figure from the total.

Estimations of Bilirubin in C.S.F. Cerebrospinal fluid, 1 ml., was added to 2 ml. buffer and to this was added 1 ml. of mixed diazo reagent and 4 ml. methanol as for serum dilutions. No blank was done and total bilirubin colour was measured against water. The calculation was:

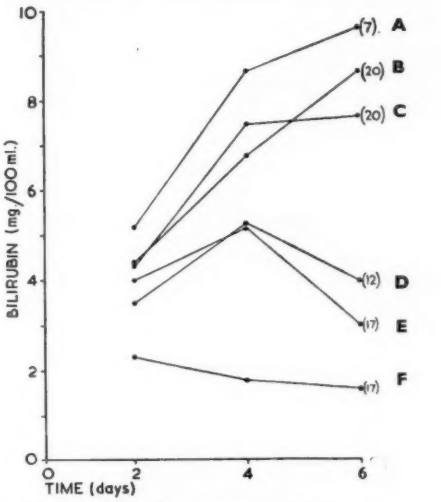
$$\frac{\text{Test}}{\text{Standard}} \times 0{\cdot}4 \times 8 \text{ mg. bilirubin per 100 ml. C.S.F.}$$

In no case was there more than 3·2 mg. of directly reacting pigment and this only in some of the mature babies showing very small quantities of bilirubin. The quantities of directly reacting pigment were usually less than 2 mg. and as these substances are not considered toxic the levels were disregarded. The total bilirubin in the C.S.F. was estimated as the figures were so low that differentiation was difficult and without significance.

Results

Fig. 1 shows the average serum bilirubin levels in the 93 babies in Phase 1 who did not develop kernikterus. They are split into 500 g.-birth-weight groups and the averages calculated and plotted. This figure shows a definite difference in the trend of the curves. The bilirubin levels of babies weighing less than 2,000 g. at birth are still tending to rise on the sixth day, whilst those of the babies in the weight group 2,000-2,500 g. are levelling out and those of the larger babies are falling by the sixth day. The babies in the highest weight group, i.e., over 3,500 g., reach their highest bilirubin levels on the second day and these have dropped by the fourth. Fig. 2 shows the weight group 2,500-3,000 g. The lowest curve is the average of the 12 babies in that weight group. The top curve is the statistically calculated maximum limits and the middle curve shows the maximum readings we obtained from the babies in that weight group.

Maximal statistical normals were calculated for all weight groups and are plotted in Fig. 3. The curves are similar to those in Fig. 2 except for the curve shown for the smallest babies, up to 1,500 g. The readings obtained from these babies showed very little spread and gave a smaller statistical standard deviation. This is the reason why the maximal statistical normal for this weight group



A—up to 1,500 g. (3 lb. 4 oz.).
B—1,500-2,000 g. (3 lb. 4 oz.-4 lb. 6 oz.).
C—2,000-2,500 g. (4 lb. 6 oz.-5 lb. 8 oz.).
D—2,500-3,000 g. (5 lb. 8 oz.-6 lb. 10 oz.).
E—3,000-3,500 g. (6 lb. 10 oz.-7 lb. 10 oz.).
F—over 3,500 g. (7 lb. 10 oz.).

FIG. 1.—Average bilirubin levels in 93 babies in Phase 1.

gives the lowest curve of the three groups of premature babies, although the average readings for this group were the highest curve. This is of importance in that there may well be a lower serum bilirubin

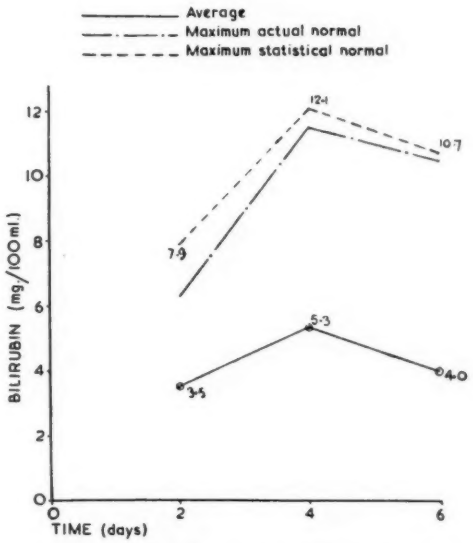
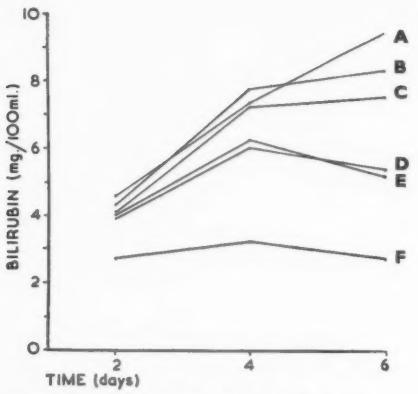


FIG. 2.—Maximum statistical normals and maximum actual normals in the weight group 2,500-3,000 g. (5 lb. 8 oz.-6 lb. 9 oz.).

level at which staining of the basal ganglia takes place in the smallest babies and would seem to add some statistical evidence for that clinical observation.



A—1,500-2,000 g. (3 lb. 4 oz.-4 lb. 6 oz.).
B—2,000-2,500 g. (4 lb. 6 oz.-5 lb. 8 oz.).
C—up to 1,500 g. (3 lb. 4 oz.).
D—3,000-3,500 g. (6 lb. 10 oz.-7 lb. 12 oz.).
E—2,500-3,000 g. (5 lb. 8 oz.-6 lb. 10 oz.).
F—over 3,500 g. (7 lb. 12 oz.).

FIG. 3.—Maximal statistical normals (all weight groups).

Fig. 4 shows the actual maximal levels of bilirubin obtained for all weight groups in Phase 1 of the investigation, against which are plotted bilirubin readings of the 12 cases of kernikterus on the days that the specimens were taken. It suggests that kernikterus is very likely to occur in any baby whose serum bilirubin level rises above 18 mg. per 100 ml. This is in agreement with the conclusions of many workers observing babies affected by haemolytic disease.

Two infants who died of kernikterus with levels below 18 mg. per 100 ml. weighed 2 lb. and 2 lb. 8 oz. respectively. They both collapsed suddenly on the sixth day, the collapse being the first sign of the condition apart from the jaundice which had not been thought to be severe. Following the collapse both babies were moribund until they died about six hours later. The samples were taken shortly before death in both cases when the bilirubin level may have been dropping rapidly. One baby had a high level of bilirubin (11·3 mg. per 100 ml.) on his third day and the inference is that the level had been very much higher in the period between the collection of the two specimens.

Fig. 5 shows the serum bilirubin levels in the 41 premature babies submitted to lumbar puncture in the first week of life who did not develop kernikterus and the 11 babies who did. The figure is interesting in that it shows samples taken from four babies who had serum bilirubin levels of over 18 mg. per 100 ml. and did not develop signs of kernikterus. At this time it was of interest to find out how high the serum bilirubin levels could rise without signs of kernikterus developing.

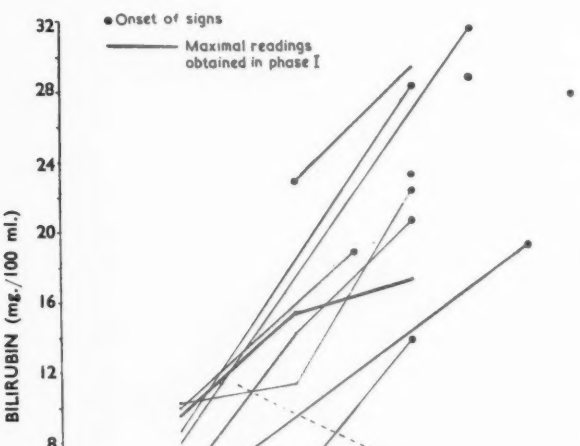


FIG. 4.—Serum bilirubin levels in babies with kernikterus.

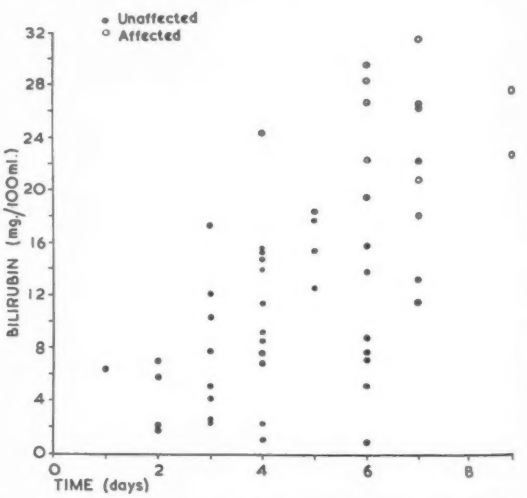


FIG. 5.—Serum bilirubin levels in unaffected and affected babies.

Fig. 6 shows the C.S.F. levels of bilirubin in the same 52 babies. There is on the whole a higher level of bilirubin in the C.S.F. of infants developing kernikterus than in the unaffected ones, but there is no correlation between the C.S.F. level of bilirubin and the appearance of signs of kernikterus.

Fig. 7 includes all babies on whom a second day bilirubin reading was obtained. The number of cases is plotted against the bilirubin levels and the levels of babies developing kernikterus is shown. It is interesting that four of the 16 babies who had

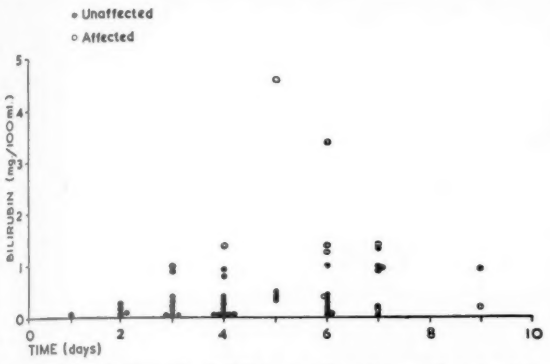


FIG. 6.—Bilirubin levels in C.S.F. in unaffected and affected babies.

second day levels of over 8 mg. per 100 ml. developed kernikterus. It seems to indicate that early biochemical prognosis of the infant likely to develop kernikterus may be possible. There were, however, two babies who developed kernikterus who had levels well below 8 mg. on the second day.

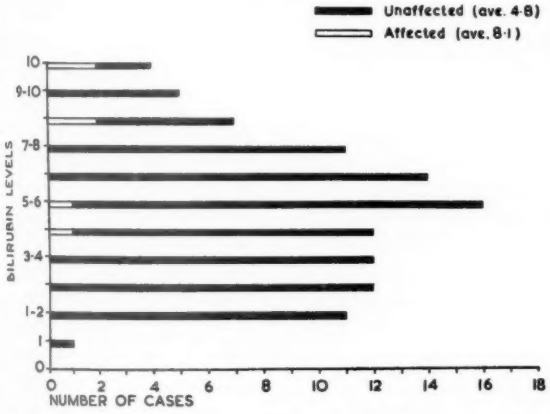


FIG. 7.—Bilirubin levels on the second day in Phases I and II (103 cases, 6 affected).

Discussion

Neonatal mortality has shown little significant change in the last 10 years when it is compared with the fall in infant mortality. Prematurity accounts for the great majority of the neonatal deaths and the proportion of spasticity amongst prematurely born babies is five times that amongst full-term babies (Asher and Schonell, 1950). The greatest mortality amongst premature babies is in the first 48 hours but, having survived this period, the premature baby is still exposed to the hazards of infection, aspiration and late effects of cerebral haemorrhage, which account for the relatively small death rate in the subsequent four weeks. There is, however, a constant increase in the mortality rate amongst premature babies towards the end of the first week of life. The majority of babies dying in this period die of kernikterus and those babies who develop kernikterus and survive are probably the major portion of the spastic, mentally defective and deaf children who are born prematurely. At Sorrento Premature Baby Unit the incidence of kernikterus in 1954 was 3·6% of all admissions and there was a 25% survival rate in those who developed the condition.

The present investigation was undertaken in the hope that it would be possible to foretell biochemically which babies would develop signs of the condition and at what levels of serum bilirubin the cerebral tissue would be damaged. There is little doubt that an infant with a serum bilirubin level higher than 18 mg. per 100 ml. runs a grave risk of developing kernikterus. Of some 350 specimens tested in the course of this investigation only 20 have been over 18 mg. %, and of these 12 babies have had kernikterus, i.e., 60% of babies reaching serum bilirubin levels of over 18 mg. per 100 ml. have developed the condition. Only the two moribund babies already discussed developed kernikterus with observed levels of less than 18 mg. %.

The treatment of hyperbilirubinaemia seems to be replacement transfusion with the sole object of reducing the bilirubin level below dangerous levels and keeping it down until liver function is sufficiently mature to convert bilirubin to the directly-reacting pigments which can be excreted. The technical difficulties of replacement transfusion at the age of a week are many but not insuperable. Replacement transfusion through the umbilical cord of a baby 5 or 6 days old is fraught with many more hazards than replacement transfusion at a few hours old. Replacement transfusion through the femoral vein using the saphenous vein as the portal of entry is technically a highly skilled procedure in a very small baby and outside the scope of many of the smaller units caring for premature babies. Therefore it would be preferable if the baby liable to develop kernikterus could be picked out early for transfer or immediate treatment using the umbilical cord.

Fig. 8 shows that the hyperbilirubinaemia was present on the second day in four of the six babies who developed kernikterus later. Replacement transfusion of the 16 babies with levels of over 8 mg. bilirubin per 100 ml. on the second day might

have prevented those four cases but not the two who had levels below 8 mg. per 100 ml.

It is not yet known exactly how the conversion of the bilirubin to the directly-reacting pigments takes place in the liver, but presumably the enzyme system responsible is synthesized in the immature liver in response to some stimulus which may well be the level of bilirubin itself. The less mature the liver the higher the bilirubin must rise before it is sufficient to stimulate production of the enzyme. If this hypothesis be true it should be possible to isolate the enzyme or some substance containing the enzyme which may then prevent the hyperbilirubinaemia.

The work of Day (1954) suggests a third possibility in the treatment of hyperbilirubinaemia. He showed that the bilirubin may be oxidized *in vitro* by cytochrome C and methylene blue, and thereby reversed the effect on the oxygen uptake of rat cerebral tissue. A similar compound with less toxic effects may be synthesized and injected into a jaundiced premature baby.

Replacement transfusion is, however, a recognized form of treatment of hyperbilirubinaemia in haemolytic disease and seems to offer the only method at present available by which toxic levels of bilirubin may be prevented and thus reduce the neonatal mortality and morbidity rate.

Summary

The present study shows the curves of serum bilirubin levels on 93 babies of all weight groups and indicates that babies under 2,000 g. (4 lb. 6 oz.) have levels still rising on the sixth day, babies of 2,000 to 2,500 levelling out and levels of babies over 2,500 g. are falling by the sixth day.

Premature babies developing kernikterus have generally higher serum levels of bilirubin and the majority have levels of over 18 mg. % at the onset of signs. Kernikterus is very likely to occur where serum levels of bilirubin rise above 18 mg. %.

There appears to be no critical level of bilirubin in the C.S.F. at which staining of basal nuclei takes place and there is no correlation between the bilirubin levels in the serum and that in the C.S.F.

It is suggested that all jaundiced premature babies should have serial bilirubin estimations, the frequency of those estimations depending on the level of bilirubin and the rate of rise of that level.

It is suggested further that replacement transfusion may be effective in the prevention of kernikterus in babies whose serum bilirubin levels are above 18 mg. % or whose rate of rise is rapid.

I am grateful to Dr. V. Mary Crosse for permission to study her patients and for her advice and encouragement during the preparation of this paper. I wish to thank Dr. A. H. Henley and the laboratory staff at Little Bromwich Hospital for their assistance, and also Miss Lane, Sister Murray, Sister Rowlly, Sister McGlynn and their staffs for their patience and invaluable help during the course of this study.

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THE RECOGNITION OF PRIMARY TUBERCULOUS INFECTION OF THE MOUTH

BY

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Primary tuberculous infection of the mouth is uncommon. One of us (Miller, 1953), in a series of 28 cases of primary infection of the skin or mucosae, described three cases which had previously been discussed at a meeting of the Royal Society of Medicine (Boyes, 1950). At that time only two other examples had been recorded in Britain (Cameron, 1939; Brand and Ballard, 1951). Since then one further case, of bovine infection, has been reported (Galloway and Horne, 1953). There are, however, references in the Continental literature, and Duken (1933) reported 10 cases in which tuberculous ulcers were found on gum or tonsils. Yet tuberculous submandibular adenitis is not uncommon, and the glands in the cases described, except that they were all of recent origin, had no special characteristics. On these grounds we thought that failure to find the primary focus in cases of recent tuberculous submandibular lymphadenitis might be due to lack of diligence in search or skill in recognition. During a study of the pathogenesis of tuberculous lymphadenitis we have taken, therefore, particular care in examining the mouth whenever we have seen a case of tuberculous submandibular adenitis of 'recent' origin, *i.e.*, one with a short history of six months and without calcium deposit, for it is only in cases of recent origin that one can reasonably expect to find a primary focus. In the absence of any evidence of earlier tuberculosis in the body, we have taken the presence of a tuberculous lesion in the mouth and tuberculous regional adenitis to indicate a primary tuberculous complex, for in clinical work we are usually denied the opportunity of observing tuberculin conversion, and therefore final proof that the infection is occurring in a non-sensitized person.

Since the first three cases were reported we have seen six others. We wish, however, to record here only seven of the nine cases, as the eighth was in a man of 58 years and merits separate description and discussion as a reinfection primary complex, and the ninth, a woman of 22 years, although we feel sure of the nature of the infection, has as yet no calcification or softening in the cervical glands. The seven cases illustrate the difficulty of recognition, the transient nature of the primary focus, and, in this series, the association of tuberculous infection with dental trauma and acute non-tuberculous alveolar abscess.

The clinical details are given in Table 1. The detailed histories are presented in the order in which the cases were seen; the tuberculous nature of the focus and the glands has been proven in every case. The ages of the patients were from 2 to 17 years; all except two (Cases 1 and 4) had a history of trauma, and these two were strikingly similar in clinical appearance (Figs. 1 and 6). Four of the other five had had teeth extracted, three following alveolar abscesses. In no case was there known contact with a tuberculous adult, and the precise sources of the infecting organisms were not discovered.

Clinical Histories

Case 1. A bright, intelligent girl almost 8 years old, the younger daughter in a lower middle class family, was first seen in October, 1948, when she was brought to hospital with a painless swelling on the ramus of the mandible on the left side. Both the girl and her parents were also aware that she had a painless ulcer on the left upper gum. Both swelling and ulcer had been present for at least three weeks. The girl had not had any other symptoms and appeared in good health. On examination, the facts were confirmed. The ulcer had destroyed the mucous membrane above the left lateral and canine incisors, the base being uneven granulation tissue and its upper limit undermining the gingivo-labial sulcus (Fig. 1). The facial gland was painless and firm, and the tonsillar gland was also enlarged. No other glandular enlargement and no other evidence of tuberculosis or other disease was present. Her tuberculin reaction (1 : 1,000 O.T.) was strongly positive; radiographs of the chest and neck did not reveal any evidence of active disease or calcification. Biopsy of the ulcer showed tuberculous granulation tissue. Streptomycin (0·5 g. daily) was

TABLE

DETAILS OF SEVEN CASES OF PRIMARY TUBERCULOSIS OF THE MOUTH IN 1948–53

Case No.	Age First Seen	Duration of Observation (years)	Probable Duration of Infection when Seen	Site of Primary Focus	Condition of Glands when First Seen	Trauma	Operative Treatment of Glands	Further Abscesses	Scars Visible (of Primary)	Ca in Gland
1	$7\frac{11}{12}$	$7\frac{1}{2}$	3 wk.	L. alveolus	Hard	None	Incision	Yes	Yes	+
2	$8\frac{10}{12}$	7	4 wk.	Tooth socket	Hard	Extractions of tooth	Incision	Yes	No	+
3	$2\frac{9}{12}$	7	8 wk.	Alveolar buccal mucosa	Softening	Stones in mouth	Incision	Yes	No	+
4	17	3	3 mth.	L. alveolus	Hard	None	Dissection (human organisms)	No	Yes	+
5	10	3	4 mth.	Tooth socket	Hard	Tooth extraction, alveolar abscess	Dissection	No	No	+
6	6	$2\frac{7}{12}$	8 wk.	Alveolar mucosa	Soft and ulcerated	Tooth extraction, alveolar abscess	Incision	Yes	No	Not yet
7	$8\frac{11}{12}$	$2\frac{5}{12}$	10 wk.	Alveolus over tooth socket	Softened	Tooth extraction, alveolar abscess	Incision	No	Yes	Not yet

FIG. 1.—Case 1. Ulcer on left alveolus extending backwards from the left lateral incisor and eroding the mucosa.

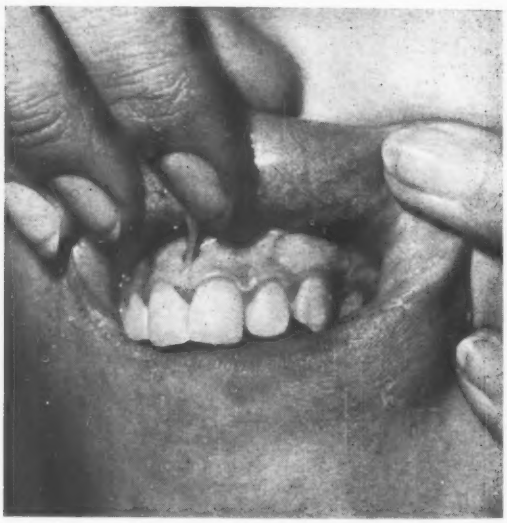

FIG. 2.—Case 1. The scar of the primary focus and the area of destroyed mucosa.

given for three weeks; during this time the ulcer healed considerably, and the glands became smaller and more discrete. She thereafter continued to attend hospital as an out-patient. The ulcer continued to heal, but it is almost impossible to say when healing was complete, as it never gave cause for complaint or anxiety. A visible scar has remained (Fig. 2). Almost a year after the streptomycin was stopped, the facial gland enlarged and softened. It was incised and subsequently discharged caseous material. Three months later, a second abscess developed in the submandibular gland and healed slowly after incision. The tonsillar gland, which was palpable, has never softened; radiological calcification is now visible.

Case 2. Aged 8, the son of artisan parents, this boy was referred to hospital with a large, painless submandibular swelling, which had appeared two weeks after tooth extraction and had been present for three weeks altogether.

On examination the mouth showed a painless circular ulcer with rather raised edges in one of the tooth sockets (Fig. 3). The boy admitted he knew about it but had not complained because it was painless. The tuberculin test (1 : 1,000 O.T.) was strongly positive. No evidence of tuberculosis was found elsewhere. Biopsy of the edges of the ulcer showed tissue characteristic of tuberculosis. Six weeks after their first appearance the glands softened and the overlying skin became red; aspirated

FIG. 3.—Case 2. Circular ulcer at site of tooth extraction.

FIG. 4.—Case 2. Three months after Fig. 3, showing permanent tooth erupting at site of primary infection.

FIG. 5.—Case 2. Eighteen months after infection the site of primary infection has been obliterated by the permanent tooth.

pus contained tubercle bacilli. Streptomycin (0·5 g. daily) was given, but only for 12 days as there was a severe reaction at the site of injection. During this time the primary focus healed rapidly but the gland abscess became larger. Three months after the boy's first visit, the primary focus was soundly healed and appeared only as a shallow circle, $\frac{1}{4}$ in. in diameter through which a permanent tooth was erupting (Fig. 4). Within 18 months all traces of the primary lesion had vanished (Fig. 5). In January, 1950, nine months after infection, the submandibular glands softened again and were removed by dissection. The wound healed by first intention; no further abscesses have appeared, but on radiological examination calcification is present.

Case 3. Aged 2, a healthy girl, the only child of young capable parents, was admitted to hospital with a softening left submandibular lymphadenitis of eight weeks' duration. An adjacent gland was also enlarged but not soft. Two weeks before the gland was first noticed, the mother had found the child with some small sharp stones from the roadside in her mouth, but as far as she could then see there was no injury. There had not been any other trauma or known contact with tuberculosis. The only other abnormal finding was an ulcer in the buccal sulcus about 1 in. long, difficult to see unless the cheek and gum were well separated, deep and sharp in outline. Biopsy showed it to be tuberculous. Pus containing tubercle bacilli was aspirated from the gland, and the abscess later incised. Unfortunately, the position of the primary focus, far posterior in the buccal sulcus, made it difficult to photograph. Streptomycin was given (0·5 g. daily) for three weeks. The effect was striking: the incision in the submandibular gland healed by first intention; the other gland became smaller, whilst the lesion in the mouth rapidly and almost completely healed. But six weeks later the second gland softened and was incised after another month of streptomycin treatment. In August, 1951, two years after the first admission, a third abscess developed. This also was incised and curetted, and there has not been any further trouble.

Case 4. Aged 17, the second of three children of artisan parents worked as a shop assistant. In January, 1953, she noticed a small lump in the left submandibular region; it was said to be slightly tender but otherwise not troublesome and she felt quite well. After three days she went to her doctor who diagnosed an abscess and gave her a penicillin injection, but the lump did not alter. She was eventually sent to hospital, but the day before going she found, quite accidentally, by pushing her tongue against it, that her gum was uneven. When first seen in March, 1953, she was a healthy looking girl with an obvious left submandibular swelling, which was composed of two enlarged glands; there was also a small gland in front and another behind the sternomastoid. They were not painful or fluctuant and the overlying skin was not adherent. In the mouth, extending from the gum over the left upper premolar and molars, was an ulcer very similar to that seen in Case 1 (Fig. 6). There was no dental caries, no history of trauma, and no known contact with tuberculosis. Her tonsils were normal and the tonsillar glands were not palpable. Streptomycin was started (1 g. daily) in the first week in April. Within a week the gland mass was smaller, the glands were discrete, but the ulcer had not changed. For the next three weeks the glands continued to get smaller, and by now the ulcer was healing. The strepto-

mycin was given daily for a month. By May 20, two weeks after the streptomycin had been stopped, the primary lesion looked almost healed and the glands were at their minimum. On June 10, 1953, she was admitted to hospital and the firm glands removed by local dissection with streptomycin cover. The wound healed by

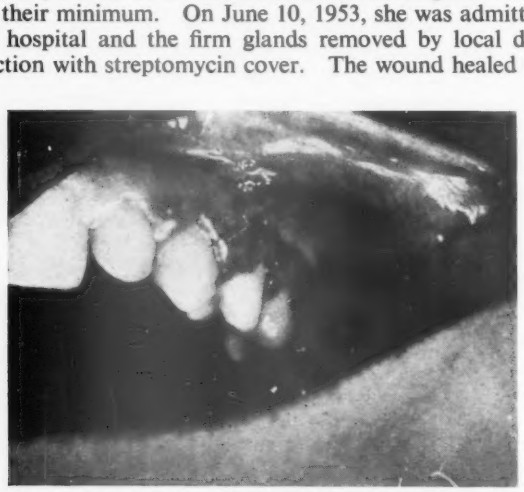

FIG. 6.—Case 4. Ulcer with irregular edges and granulating base over upper gum extending back from left premolar (March, 1953).

first intention. When seen one year later, there had been no further trouble or complaint, the scar in the neck was firmly healed, no glands were palpable, but radiological calcification was present near the site of operation, and a scar (Fig. 7) has remained on the gum at the site of the primary focus, very similar to that seen in Fig. 2.

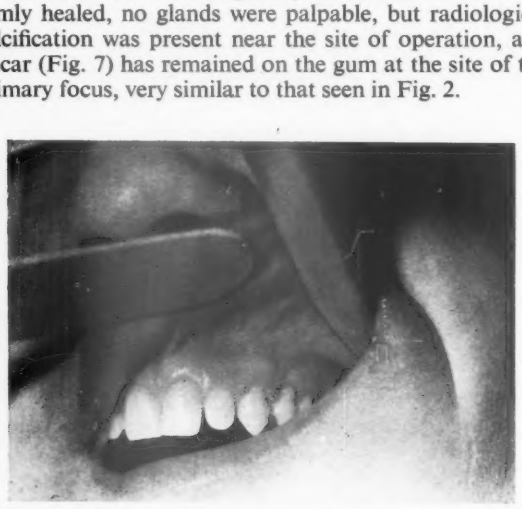

FIG. 7.—Case 4. Scar remaining at site of primary infection.

Case 5. A sturdy boy aged 10, from a miner's family, five months before attendance at hospital suddenly developed a tender swelling of the left cheek, and after three days was taken to a dental clinic where an alveolar abscess was incised. A few days later four teeth were extracted, and three weeks afterwards another swelling, this time painless and firm, appeared in the submandibular region. At this time another child was very ill with pink disease, and as the boy's lump was painless and he seemed well, six weeks elapsed before he was taken again to the dentist, where he was examined and radiographs taken. But the swelling slowly grew larger, and the family doctor sent the child to hospital when the swelling had been present for about 15 weeks.

On examination he had a firm, painless mass in the left submandibular region. Over the outer aspects of the tooth sockets in the left upper jaw there was a small, quite inconspicuous area which looked like an unhealed area of granulation tissue, but no definite ulcer. The tuberculin test was positive. Radiological examination did not reveal any evidence of tuberculosis in the chest or calcification in neck or abdomen. At first there was some discussion whether biopsy of the small area would be profitable, but when it was done examination of the specimen revealed the histological picture of tuberculous infection. The boy was then given streptomycin for six weeks, with considerable reduction in the size of the gland mass and complete healing of the granulating area. For the next two months he was well but the gland remained unchanged, so almost a year after the alveolar abscess the glands were removed by dissection and found to be caseous. The wound healed by first intention, and two years later there has not been any further trouble.

Case 6. Aged 6, the second and younger child of a miner, living in a large colliery village in Northumberland, was admitted to hospital on September 7, 1953, suffering from tuberculous meningitis of about one week's duration. On June 30, eight weeks before the onset of tuberculous meningitis, she had toothache and an alveolar abscess. One week later the tooth was removed and the swelling of the face disappeared. There had also been a tender, firm, submandibular lymphadenitis, but this, though losing its tenderness, did not disappear. After another week, the mother consulted her doctor who said that the swelling was in a gland and that an abscess might ensue. In another few days the family went for a fortnight's holiday, but the child was 'off colour' and the swelling slowly became larger. On return from holiday, the doctor was again consulted, and this time an ulcer was found at the site of the tooth extraction in the sulcus beneath. On August 8 and 9, the submandibular swelling was poulticed and the next day was incised. It did not heal, the skin around the incision became eroded, and on August 21 tubercle bacilli were recovered from the pus. For another 10 days the child seemed well, but early in the morning of September 1, she woke and vomited; the next day she vomited again, was unhappy, refusing her food. She continued in this way for five days, becoming thinner and developing headache, and she was sent to hospital with the clinical diagnosis of early tuberculous meningitis.

On examination she was thin, rather quiet and anxious, but fairly alert and quite responsive; some neck and back stiffness was detected. In the submandibular area on the left side there was an ulcer with a sloughing base and thin undermined edges; adjacent lymph nodes were hard and discrete; the spleen was palpable 1 in. below the costal margin, but no other abnormal signs were found. The tuberculin test (1 : 1,000 solution of O.T.) was positive, and the spinal fluid contained 300 lymphocytes and an excess of protein (160 mg. %). In the sulcus

between the cheek and the alveolar margin at the site of the extraction, was a painless ulcer 1 in. long, with irregular sharp edges and a yellow base, seen only when the cheek was held away from the gum (Fig. 8), the inner margin of the ulcer extending on to the alveolar margin at the site of the tooth. In the surrounding mucous

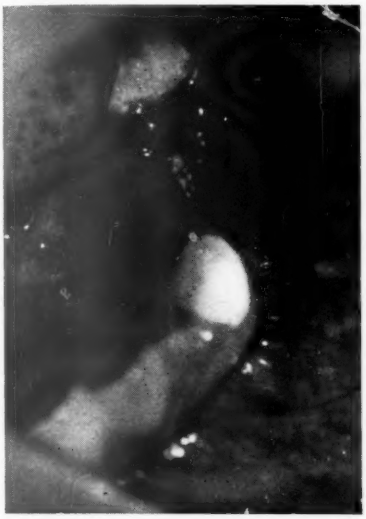

FIG. 8.—Case 6. Lesion in mouth, ulcer in gingivo-labial sulcus. Two small yellow ulcers are visible on the extreme right of the picture.

membrane, several small yellow-grey nodules, about 1 mm. in diameter, were scattered irregularly. These seem comparable to the satellite nodules sometimes seen in natural primary infection of skin, or in B.C.G. inoculation, and described in the mouth by Horne (1953) in his case report. Fortunately, the child made a straightforward recovery from the meningitis, and at the same time the lesions in the mouth and gland healed. On treatment with streptomycin and P.A.S., within two weeks the mouth ulcer was smaller, the sloughing yellow base was clean, and progress continued until healing

FIG. 9.—Case 6. Site of primary infection without scar formation or trace of previous ulcer three months later and approximately five months after infection.

was complete without scarring. Thus, by the time the meningitis was cured, the site of the primary infection had disappeared (Fig. 9) leaving no trace other than the scar of the gland abscess in the neck. Within six months, a gland adjacent to the original abscess enlarged and was removed together with the scar of the first lesion. She is still well, two years later, and calcification is now visible at the site of the gland.

This child undoubtedly had an alveolar abscess and acute submandibular adenitis. Tooth extraction was followed by primary infection in the tooth socket and sulcus, and tuberculous meningitis subsided within eight weeks. It is the only case in which we have seen satellite nodules in a primary lesion on a mucosal surface.

Case 7. A boy aged 8, the elder of two children, was admitted to hospital on December 19, 1953, with a softening gland abscess well forward in the right submandibular region. He had been ill since the morning of October 29, when he awoke to find the right side of his face tender and swollen, and a small tender gland under the ramus of the mandible, on the same side. This swelling became bigger and the gland remained tender for 48 hours. Two days later he was aware of a purulent discharge in his mouth, and afterwards the swelling of the face rapidly disappeared but the gland remained enlarged until his dentist referred him to hospital where he had a tooth removed. But the alveolar abscess

FIG. 10.—Case 7. Irregular granulating area on gum in region of extracted tooth.

continued to discharge and the tooth crater did not heal satisfactorily. A fortnight later a biopsy revealed tuberculous granulation tissue in the tooth socket. Slowly the submandibular gland enlarged, and, when first seen in the Children's Department on December 15, was soft with early reddening of the skin. In the mouth over the gum of the right upper canine was an irregular granulating area (Fig. 10), in the centre of which a bead of green pus exuded through a sinus. He was not in good general health, but no other lesions were present and there was no other evidence of tuberculosis. On December 24 the gland swelling was incised; the pus contained tubercle bacilli and the wall of the gland abscess showed caseating tuberculosis. He was given streptomycin (1 g. daily) and isoniazid (I.N.H.) (250 mg. daily). There was an almost immediate improvement in his general health, the gland

incision healed, and the granulating area on the gum diminished. This therapy was continued for a month, and I.N.H. for one month more. At the end of this time a small granulating area still showed on the gum, but the scar in the gland had firmly healed. When seen in August, 1954, there was a small sequestrum in the bone; this was removed, and later an ectopic canine tooth erupted.

Discussion

These seven cases all present the combination of a painless tuberculous ulcer in the mouth and a regional tuberculous lymphadenitis. No evidence of other primary infection or earlier tuberculous lesion was present in any patient. The only proof of primary infection lacking is knowledge of the tuberculin state of the patient before the appearance of the complex. But we have already made the point that this knowledge would be very exceptional in clinical work.

In no case could we establish contact with an infectious adult, but in the only case where the organisms were typed they were human in origin (Case 4).

The seven cases fell into two groups: five with a history of trauma and two without it. In four of the first group the trauma was that of dental extraction, and three of these children had also alveolar abscesses and a preceding acute lymphadenitis; the other (Case 2) followed the extraction of carious teeth without acute abscess formation. The primary lesions following dental extractions were at the site of the tooth socket or in the sulcus between the gum and the cheek, ranging in shape and size from a circular lesion in Case 2 to a long, irregular ulcer in Case 6 and Case 3. In one case at least (Case 5) the lesion was so small and apparently insignificant that there was doubt if a biopsy would be worth while, and we could not obtain a satisfactory photograph. In one (Case 7) the presence of tuberculous granulation tissue was masked by the discharging alveolar sinus. These lesions have quite disappeared as they healed or as permanent teeth have erupted, and their presence could not have been suspected later.

The two cases without history of injury were different from those just described, but strikingly similar to each other (Cases 1 and 4), with a large painless ulcer on the gum above normal intact teeth. In each case the gland swelling brought the patient to the family doctor, although both girls knew the lesions were present in the mouth. These lesions healed satisfactorily, but have left an outline of their margins on the alveolar mucous membrane which must correspond to the scar seen in cases of skin tubercle where there is no history of trauma (Miller, 1953).

Thus, it seems that any chronic lesion in the mouth, any area of dental trauma which fails to heal completely, or any area of granulation tissue, is under suspicion and should be examined histologically. If there is also swelling of the glands, the possibility of primary tuberculosis should certainly be considered, and we think that a more adequate search whenever submandibular glands have been recently involved would reveal more cases of primary foci in the mouth. But the primary focus must sometimes be very small and inconspicuous, for we have seen several cases within the period of this study when the glands were recent and no other evidence of tuberculosis existed, and yet, despite the most careful search, we could find no trace of a primary focus in the mouth.

The glands in this group of cases were all in the submandibular area except in Case 1 where the facial was the gland first involved and then the tonsillar. In five cases the glands were hard and discrete when first seen. Two were removed before softening (Cases 4 and 5), and these have not given rise to further trouble. In the other five cases the glands softened before surgical treatment was undertaken. In four of these, incision was the only treatment possible, and in all four further abscesses formed in neighbouring glands. In only one case has there been any evidence of haematogenous lesion in the form of meningitis appearing within eight weeks of infection. Cases 1-5 have evidence of calcification at the regional glands, but no other calcification in the neck, chest, or abdomen; Cases 6 and 7 have not yet developed radiological calcification in the regional glands but may yet do so.

Summary

The histories of seven patients aged from 2 to 17 years are given, and the reasons are advanced for considering that they are suffering from primary tuberculous infection in the mouth. The characteristics of the primary lesions are described, and the point is made that they may disappear leaving no scar. If so, the origin of the glands cannot be determined afterwards. There is some evidence that glands should be removed when firm, for if they spontaneously soften, subsequent secondary abscesses are common.

We wish to record our thanks to our colleagues in the Departments of Bacteriology, Pathology, Radiology, and Surgery in the Royal Victoria Infirmary, and to the Director of the Department of Medical Photography of King's College.

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WHOOPING COUGH ENCEPHALITIS

BY

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It is the purpose of this paper to report a case in which fatal convulsions occurred during convalescence from whooping cough, at a time when paroxysms of coughing were absent. This case is not unique, a similar one having been reported by Hiller and Grinker (1930). These authors point out that while air embolism or circulatory stasis may be a satisfactory explanation of convulsions associated with severe paroxysms of coughing, some other mechanism must be responsible for convulsions occurring apart from such paroxysms. A study of the case reported below suggested an alternative explanation.

Case Report

The patient, a girl aged 3 years, was admitted to the Connaught Hospital on September 3, 1951. The child was born by a normal full-term delivery without any jaundice. She had been quite well until this infection with whooping cough. She had been inoculated with diphtheria toxoid at 18 months, but had not received any of the pertussis vaccines being used at the time.

There is no history of fits on either the maternal or paternal sides of the family, the other two children, both boys, being quite well and also free from fits.

Six to seven weeks before admission, the child developed a cough which was diagnosed as whooping cough with mild paroxysms (these were never very severe). Two weeks before admission, the mother noticed that the child was a little more fractious than she had been previously, with a slightly puffy face and with slightly swollen glands in the neck. The puffiness and swelling had disappeared two days later. The day before admission the child seemed very well and was helping her father in the garden and had no paroxysms of cough, although an occasional isolated cough was heard. She was put to bed and although the parents heard an occasional cough during the night, the mother is quite certain that there were no paroxysms. The following morning the child vomited twice and was listless and drowsy, lying curled up in a chair with no appetite. On the afternoon of admission, she appeared dazed and drowsy and would not respond to questions. On the way to hospital in an ambulance, she started to have a fit which lasted for about 15 minutes. She was given phenobarbitone, grain 1, and the convulsions ceased, but she remained stuporose.

On examination, she was dazed. The head and eyes were turned to the left side, there were no convulsions, but the arms were held stiffly and twitched slightly. The tendon reflexes were present and equal, but the abdominal reflexes were absent. The right plantar response was not obtained and the left was flexor.

At 11.25 p.m. she started to have a fit. The fit started on the left side of the face and the left arm and later became generalized. She was given soluble phenobarbitone, grain 1, intramuscularly. At 11.50 p.m. the fit was still continuing in the face on both sides and in both arms though it was less severe in the legs. She was given paraldehyde, 2 ml., intramuscularly.

On September 4 at 1 a.m. she was still having convulsions, but they were now entirely confined to the eyes, left arm and left leg, and they were not as violent as before. Her respirations were rather irregular and shallow. Her pulse was very rapid. At 7.30 a.m. she had another fit, but this time it was entirely right sided.

At 6 p.m. on the same day, she seemed drowsy and lay curled up. She did not cry when moved, but curled up again. She did not respond when her name was called but the ward sister said that she spoke rationally once or twice during the day. The abdominal reflexes were now present but sluggish. The knee and ankle jerks were present and equal but the knee jerks were sluggish. The plantar responses were both flexor. A lumbar puncture was performed, which yielded clear C.S.F. under a pressure of 230 mm. Crystalline penicillin, 100,000 units, were given intrathecally. At 8.30 p.m. the child was more alert and was talking rationally. On September 5, she was dehydrated and stuporose, she had a left hemiplegia and could not close the left eye. The left arm and leg were spastic and the abdominal reflexes were absent. The knee and ankle jerks were present and equal. The right plantar response was not obtained and the left was extensor. Pin-prick was appreciated in the left foot and leg, but she did not withdraw the leg. The C.S.F. was under a pressure of 220 mm., there were 80 lymphocytes per c.mm. and 50 mg. of glucose per 100 ml.

She was given a gastric drip and put in an oxygen tent; chloramphenicol, 0·5 g., was given six hourly and the penicillin, 100,000 units, was continued six-hourly intramuscularly.

By the afternoon, she seemed rather better, her colour was improved and her breathing was quieter. She moved the left arm and leg when pricked. At 5.30 p.m. she suddenly went blue and the right arm became rigid. Her heart continued to beat for about 15 minutes, but in spite of artificial respiration she died.

Necropsy. The cardiovascular system showed no abnormality apart from a few petechial haemorrhages on the epicardium.

The trachea and bronchi contained a little viscid mucus.

The lungs showed small patches of collapse at the bases with sub-pleural petechiae. The mediastinal lymph nodes were slightly enlarged. The liver and spleen were congested, the spleen being slightly larger than normal.

The mesenteric and pre-aortic lymph nodes were slightly enlarged. The stomach and intestines were normal. The pancreas was congested. The kidneys appeared normal. The thyroid and suprarenal glands were normal.

Histology of the spleen revealed congestion of the pulp. The lymph nodes showed chronic inflammatory reactive changes.

The brain was fixed in formalin and then examined. It weighed 1,555 g. and was unusually pale. It showed great swelling of the cerebral convolutions and the cerebral hemispheres were softer than normal.

On cutting through the brain, the white matter of both hemispheres was extremely soft, especially at the level of the thalamus. The softening reached its maximum on the right side at the level of the posterior horn of the lateral ventricle. In this region, the white matter was peppered with dilated, small blood vessels. Many of these vessels were surrounded by an indistinct, brownish halo less than 0·05 cm. in diameter. In addition to the brownish haloes, there was a general discoloration, mainly occupying the centrum semi-ovale, and not extending intto the digitate white matter. The grey matter in the depth of the sulcus between the right inferior frontal convolution and the orbital gyrus appeared to be softened.

Histology. Throughout the cerebral hemisphere there was cuffing of blood vessels with lymphocytes, up to 10 layers thick. The cuffing was most prominent in the cerebral cortex of all areas, was much less marked in the white matter and was practically absent from the cerebellum. The cuffing was very prominent in all parts of the thalamus (Fig. 1 and 2) and the zona incerta, but much less obvious in the lentiform and caudate nuclei. There were occasional heavily cuffed vessels in the ventral part of the internal capsule, especially anteriorly. In the mid-brain, cuffing was marked around vessels in the superior colliculus and in the substantia nigra; in the pons, the periaqueductal grey matter was most involved (Fig. 3), but a few vessels in the floor of the fourth ventricle were cuffed as were also perforating vessels deep within the brain stem.

Frequently the lymphocytes extended beyond the perivascular space into the surrounding tissue, which

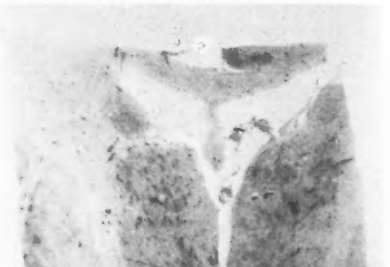

FIG. 1.—Thalamus, showing greatly increased prominence of vessels. The white matter is little affected. Nissl.

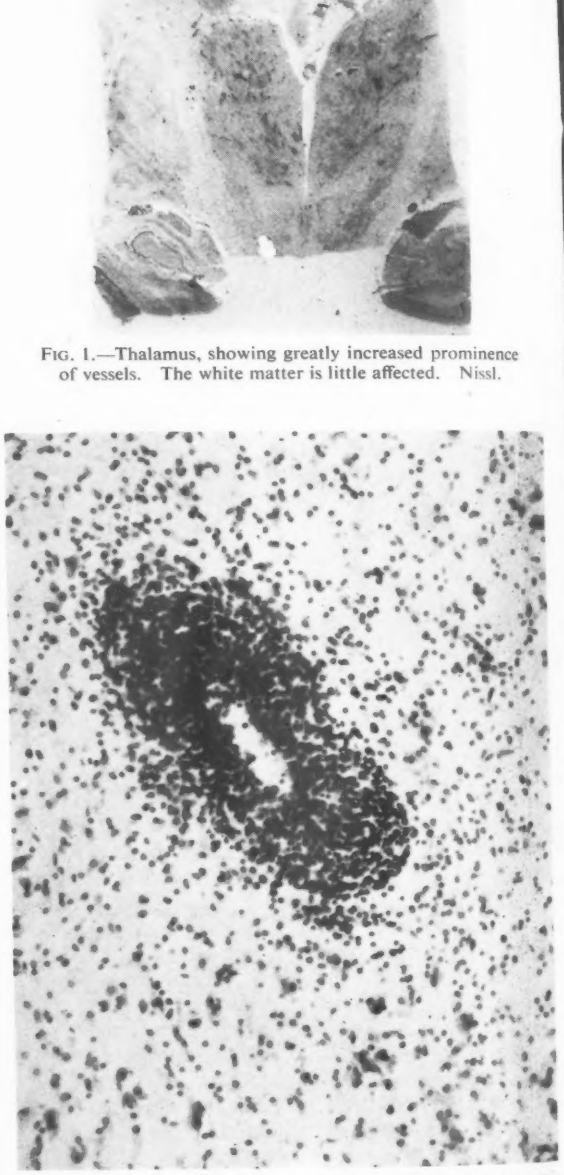

FIG. 2.—Thalamus, showing severe perivascular lymphocytic cuffing with activation of astrocytes around vessels and wandering of lymphocytes into tissues. Nissl × 112.

showed activated astrocytes and proliferated microglia over a wider area. It was never possible to demonstrate definite infiltration or actual injury of the walls of vessels.

The right insula, both central regions and the dorsal convolutions of both frontal lobes showed extensive but patchy palings affecting the superficial layers or the

whole thickness of the cortex (Fig. 4). Within these palings, the nerve cells showed a fine stippling of the chromatin of the nucleus, though sometimes larger globules of chromatin were present. The nucleolus was always enlarged and stained metachromatically. The cell body was sometimes of normal shape or slightly swollen, with an indistinctness or ground glass-like homogenization of the Nissl substance; at other times the cells were greatly swollen with a complete loss of Nissl substance and vacuole formation, recalling Nissl's 'water change'. Other cells showed more advanced degeneration, the nucleus being coarsely stippled and the cell body barely visible. Only very occasionally was encrustation of nerve cells seen. No marked change in the interstitial elements was observed. Of the various areas of cortex showing palings, that around the sulcus between the right middle and inferior frontal convolutions was the most severely affected.

The Sommer sector and endfolium of both Ammon's horns showed intense neuronophagia and ischaemic degeneration of nerve cells, with many rod cells and amoeboid microglia and astrocytes showing Alzheimer's amoeboid change (Fig. 5). There was marked lymphocytic infiltration of the leptomeninges (Fig. 6).

Discussion

There appear to be in this case two distinct pathological processes: (1) A meningo-encephalitis characterized by severe lymphocytic infiltration of the subarachnoid space and thick perivascular cuffs of lymphocytes; some of the latter are infiltrating diffusely into the perivascular cerebral tissue, which shows a glial reaction suggestive of the effects of oedema. (2) Focal areas of selective parenchymal degeneration, considered to be typical of the effects of cerebral anoxia (Scholz, 1949), comprising the cortex of the right insula, both central regions and the dorsal convolutions of both frontal lobes, together with the endfolium and Sommer's

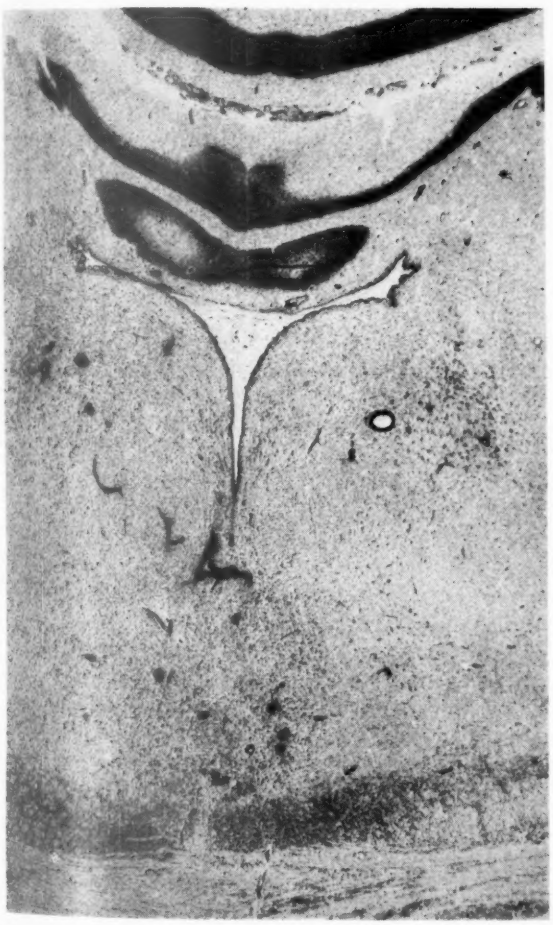

FIG. 3.—Upper part of pons, showing perivascular cuffing in periaqueductal grey matter. Nissl × 11.

FIG. 4.—Right superior frontal convolution, showing paling of superficial layers of cortex, especially in depths of sulcus. Nissl × 40.

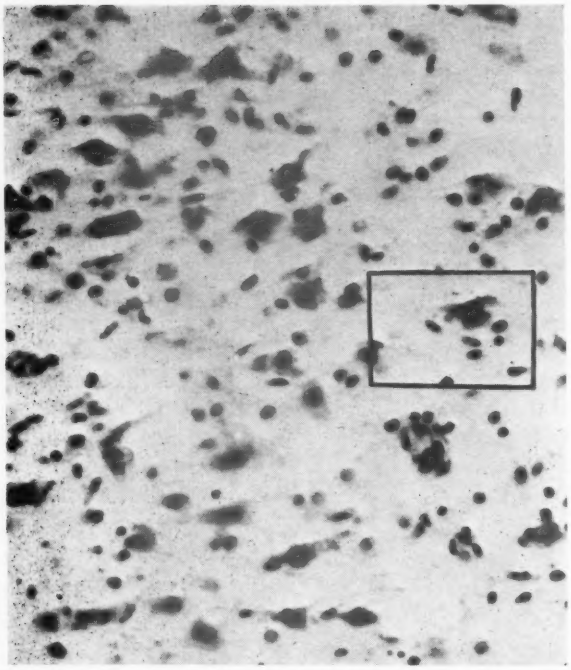

FIG. 5.—Ammon's horn, showing ischaemic nerve cells and microglial rod cells. The rectangle encloses an encrusted, ischaemic nerve cell. Nissl × 300.

FIG. 6.—Right pre-central region, showing heavy infiltration of the leptomeninges with lymphocytes. Nissl × 39.

sector of both Ammon's horns. The presence of many nerve cells showing acute ischaemic and homogenizing degeneration suggests that the anoxic episode responsible must have occurred within the last few days of life. While it is possible that the severe perivascular infiltrations may have caused minor circulatory disturbances, it seems unlikely that these were responsible for the sudden simultaneous development of widespread, very severe, focal anoxic lesions, confined to the cerebral cortex and Ammon's horn. On the other hand, just such a pattern of lesions is described by Scholz (1951) as an occasional finding in children dying in status epilepticus. Our patient was admitted in status epilepticus and the anoxic lesions are of an age consistent with having developed at this time. Their presence amply explains the depression of consciousness and focal neurological signs which followed the convulsions. It seems reasonable, therefore, to suggest that the anoxic lesions were caused in some way by the epileptic attack. If this view is accepted, it may be felt that some of the similar lesions seen in cases of 'whooping cough eclampsia' and regarded by Husler and Spatz (1924) as toxic and by Neubürger (1925) as the result of air embolism may in fact be the result of the convulsions. It may be significant that the neurological symptoms included convulsions in all reported cases of whooping cough eclampsia showing this type of selective parenchymal degeneration.

It remains to postulate a cause of the convulsions. In those cases in which fits supervene at the height of the whooping cough, a variety of causes may be put forward including toxaemia, air embolism and anoxia from respiratory embarrassment during a paroxysm. Indeed, as has recently been mentioned by Meyer, Beck and Shepherd (1955), severe epileptic convulsions may be precipitated by fevers, acute gastric infections and allergic crises. To this list, these authors add an important case in which status epilepticus complicated Still's disease. The patient survived the convulsions in a demented state for 12 months. By post-mortem examination the authors were able to demonstrate lesions which they consider to be associated with the original attack of status epilepticus. In this, they were guided by the topography and the histological character of the changes. Our case would probably have shown similar changes if survival had been equally prolonged. The cause of the convulsions in these

cases often defies detection. Meyer and his collaborators were unable, in their case, to find any obvious nexus between the convulsions and any preceding event in the medical history. We are, perhaps, more fortunate. Examining the brain only two days after the onset of the convulsions, we were able to show meningo-encephalitic changes, such as might have been present in the case of Meyer *et al.* at a similar stage in its evolution. These changes may well have reflected the leucocytosis so well recognized in whooping cough (Seitz, 1925). It is remarkable that they have not been more frequently encountered in the brain. The 'encephalitic' changes in the case of Askin and Zimmerman (1929), much quoted in the American literature, included foci of mononuclear cellular infiltration and mononuclear and polymorphonuclear leucocytes in the sub-ependymal tissue of the lateral ventricle; nevertheless, the absence of perivascular cuffing or meningeal exudate prevents us from comparing the case too closely with our own. Habel and Lucchesi (1938) report early lymphocytic cuffing in the brain in one of seven cases subjected to necropsy. They state that it is evident that certain patients have 'definite' encephalitis as the underlying cause of the convulsions from the fact that convulsions occur when paroxysms are mild and bronchopneumonia is absent. They do not, however, give any examples or references to examples.

Considerable interest attaches to the report by Fonteyne and Dagnelie (1932) on the effects of intracerebral injection of *H. pertussis* toxin in guinea-pigs. The changes included (1) a very severe leucocytic meningeal reaction with predominance of polymorphonuclear leucocytes, (2) congestion of vessels, with numerous large perivascular cuffs of polymorphonuclear leucocytes and small lymphocytes in the cerebral peduncles and basal ganglia. It seems possible that in our case also the encephalitic changes resulted from the action of *H. pertussis* toxin. An alternative possibility is that the encephalitis was caused by some unknown and unrelated virus to which the whooping cough may or may not have lowered the resistance of the patient. In any case, the fact remains that a true encephalitis may occasionally occur during convalescence from whooping cough and cause convulsions in the absence of paroxysms of coughing; these convulsions, if sufficiently severe or accompanied by a sufficient degree of respiratory embarrassment, may cause anoxic degeneration of nerve cells especially in the cerebral cortex and Ammon's horn, with severe depression of consciousness, which may be immediately or rapidly fatal or lead to the permanent neuropsychiatric sequels (dementia, hemiplegia or generalized rigidity) well recognized (Ford, 1952) as following pertussis encephalopathy.

Summary

A case is reported in which convulsions fatal in 36 hours developed during convalescence from whooping cough at a time when there were no paroxysms of coughing.

Pathological examination of the brain showed very severe lymphocytic infiltration of the meninges and perivascular spaces constituting a meningo-encephalitis, together with degenerative lesions of an anoxic type, in scattered areas of cerebral cortex and in the Ammon's horn.

It is suggested that the meningo-encephalitis was responsible for the convulsions and that the anoxic changes were the result and not the cause of the fits. This contrasts with the situation in cases of whooping cough eclampsia where fits follow a paroxysm of coughing. In these cases anoxia, from air embolism or cerebral venous stasis, is usually considered to be the cause both of the convulsions and the nerve cell changes.

It is a pleasure to record our indebtedness to Professor Alfred Meyer for helpful advice during the investigation of this case.

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HYDROPS FOETALIS SUCCESSFULLY TREATED BY EXCHANGE TRANSFUSION

BY

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Cases of Rhesus incompatibility resulting in the condition known as hydrops foetalis do badly. Mollison and Cutbush (1954) state 'it is doubtful if infants born with ascites ever survive', and it is difficult to find any record of survival. Heilig, Tudor, Smith and Platou (1948) report two cases of hydrops, one of which survived with a hemiplegia. Van Loghem, van Bolhuis, Soeters and Veeneklaas (1949) describe, among 160 cases of erythroblastosis foetalis treated with exchange transfusion, four infants with hydrops. Three of these died but the fourth survived. This child, however, had no ascites, only oedema of the umbilical cord, hands and feet. The following case is probably unusual, but worth reporting because of the initial hopeless prognosis and the ensuing remarkable recovery.

Case Report

The mother was aged 35 years and had had three previous pregnancies. She had a normal child in 1947, and in 1950 was delivered of a stillborn child at the eighth month: unfortunately there are no details available about the stillbirth. A third child was born at full term in 1952. She was known to have group O Rh-negative blood, and during her third pregnancy in 1952 antibodies were found in the blood at 20 weeks, and subsequently at the thirtieth and thirty-fifth weeks, when the anti-D antibody was present to a titre of 1 in 16. The father's blood was examined at this time and found to be group O homozygous Rh positive. The third child was born at term and was noticed to be slightly jaundiced soon after birth. The jaundice deepened within the first hour and cord blood had a positive Coombs test and a haemoglobin content of 92% Haldane two hours after birth, when 500 ml. of group O Rh-negative packed red cells were given. This child is now 3 years old and seems normal in every way.

In 1955 the mother again became pregnant. Rhesus antibodies were present in her blood at 22 weeks and at 32 weeks. At 34 weeks albumin agglutinating anti-D was present to a titre of 1 in 16, and at 37 weeks to a titre of 1 in 32. On the second occasion a trace of saline anti-D was also present.

On June 16, 1955, spontaneous delivery complicated by delay in the second stage took place. The delay was found to be due to impaction of the child's ascitic abdomen in the vagina of the mother. The child was a girl weighing 9 lb. 2½ oz. There was no cyanosis or jaundice, but the child was pale with oedema of the feet, legs and vulva, and a large protruding abdomen measuring 18 in. at the widest part. The abdominal wall was so tense that the liver and spleen could not be felt. The heart sounds were present and there were no murmurs. There were medium râles all over both lung fields. The Coombs test was positive on the cord blood, which was group O Rh-positive and had a haemoglobin content of 68% Haldane.

In spite of the child's discouraging appearance, exchange transfusion with packed group O Rh-negative cells was begun, one hour after birth. It was attempted by the umbilical route, but after much technical difficulty, almost certainly due to the stretching of the umbilical vein by the ascites, this had to be abandoned after only 66 ml. of packed cells had been given and 55 ml. of blood removed. Eventually exchange transfusion was carried out by cutting down on the left saphenous vein at its point of entry into the femoral vein. In all 442 ml. of packed cells were given, and 432 ml. of blood removed. Of this, 60 ml. were removed at the end of the exchange as an emergency measure because the child became cyanosed and distressed, although continuous oxygen was being given by nasal catheter. By the end of transfusion the moist sounds had completely disappeared from the chest but the respiratory excursion was still very small because of the ascites. Transfusion was not completed until about 10 hours after birth.

The following day the child's general condition was fairly good and the chest was clear, but the legs and thighs were more oedematous than at birth and there was slight jaundice. The abdomen was less tense, measuring 17 in., and both the liver and spleen could now be felt. The liver was enlarged to two fingerbreadths, and the spleen to three, below the costal margin. Haemoglobin was 90% Haldane, direct Coombs test negative, serum bilirubin 3·8 mg. and serum proteins 5 g. per 100 ml. (albumin 3·6 g. and globulin 1·4 g.). Intramuscular terramycin was given for four days as a prophylaxis against any infection that might have been introduced at the time of transfusion. Feeding was attempted on

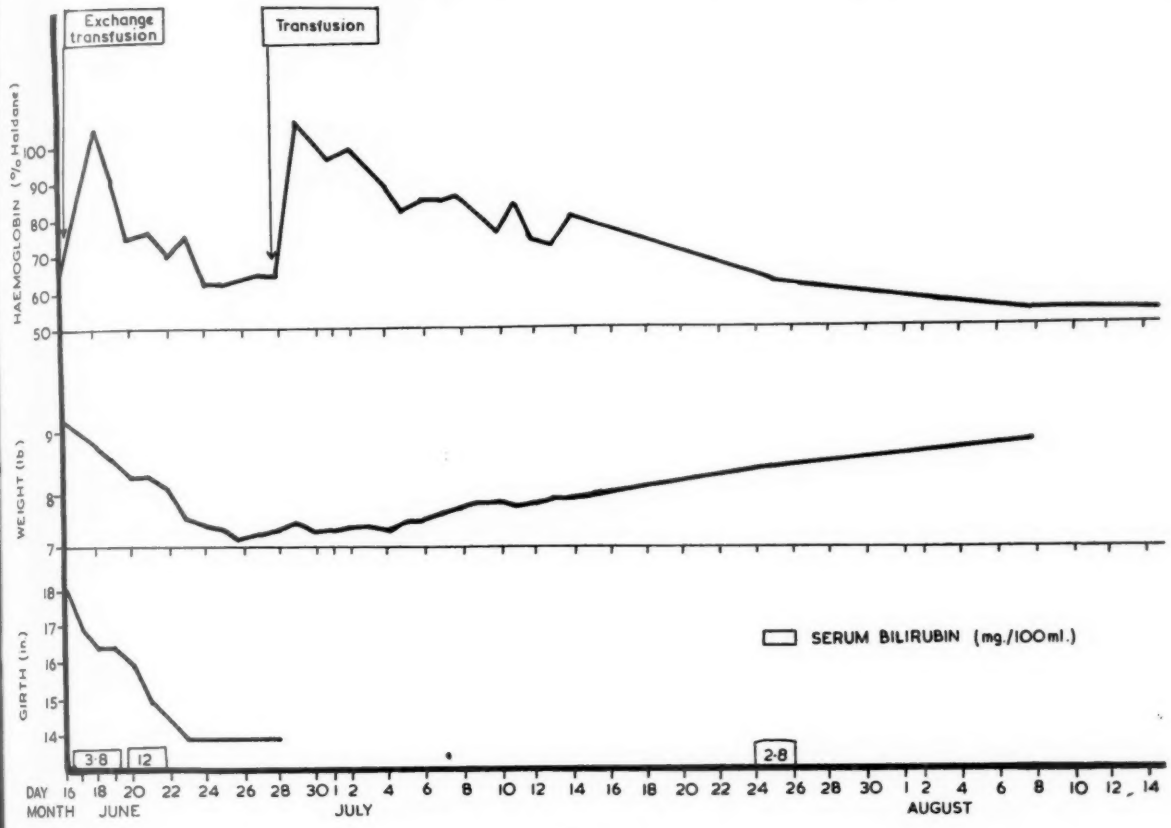

FIG. 1.

the second day and by the third day she was taking small amounts of milk and water fairly well.

The ascites slowly disappeared. The daily measurement of the child's girth and the daily haemoglobin estimations and weights are given in the figure. By about the seventh day the jaundice reached its maximum (approximate maximum total serum bilirubin 12 mg. per 100 ml.), and then faded gradually. On the ninth day the ascites had disappeared. By the thirteenth day the liver was a little smaller and the spleen definitely smaller, being only 1 in. below the costal margin, but the haemoglobin had fallen to 66%. Because of the increasing anaemia, 105 ml. of group O Rh-negative compatible blood were transfused through a scalp vein. After this, haemoglobin rose to 106% and gradually dropped again without any further increase in jaundice. On the thirtieth day when the child was discharged home the haemoglobin had fallen to 82%. At this time she was well and looked normal apart from some green staining of the optic sclerae. The spleen was now ½ in. below the costal margin and the liver 1½ in. below.

The child has been seen several times as an out-patient and is doing well. When she was last seen on October 3, 1955, at the age of 3½ months, the spleen was just palpable and the liver was only ½ in. below the costal margin: haemoglobin was 74% and there was no jaundice. Her weight was 9 lb. 13 oz. There have never been any signs or symptoms of kernikterus.

Summary

A case of hydrops foetalis with gross ascites which did well after exchange transfusion is described. Although the child was in severe heart failure at birth, the degree of anaemia was not so great as is usually found in these cases. This fact may partially account for the recovery.

I should like to thank Dr. Charles Harris for permission to publish this case.

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LARYNGEAL STENOSIS WITH TRACHEOSTOMY TREATED BY HEMI-LARYNGECTOMY AND RECONSTRUCTION OF THE LARYNGEAL ORIFICE

BY

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The patient, a girl, 2½ years old, was born in Jamaica, the birth weight being 7½ lb. Pregnancy was normal, with the delivery at full term. There was no dyspnoea or cyanosis at birth. Stridor and attacks of 'cyanosis' started soon after birth, especially with feeds, culminating with a very severe attack at 11 months. A direct laryngoscopy was performed, and the larynx was 'probed'. The condition deteriorated, and an immediate tracheostomy was performed.

The child arrived in England at the end of June, 1955, when she was admitted to the Victoria Hospital for Children, Tite Street, London. Here a direct laryngoscopy was performed by Mr. Pereira, when a very stenosed larynx was seen, with no details of the true cords observed.

On July 19, 1955, she was transferred to The Hospital for Sick Children, Great Ormond Street. On admission, she appeared in good general health. The tracheostomy tube was *in situ*.

On July 21, 1955, a direct laryngoscopy was performed, and the earlier findings were confirmed. The laryngeal orifice was extremely small, and no details of the left true cord could be seen at all. The whole of this side of the larynx appeared to be fibrosed. By angling the laryngoscope, the right true cord was seen in part, and this appeared to be normal. The epiglottis was normal. It was quite impossible to pass even a suckling bronchoscope through the larynx—a probe was the only instrument it would admit.

A trial of respiration without the tracheostomy tube was then made, but it was obvious that the child could not breathe without the tracheal stoma being patent, and the tube was reinserted.

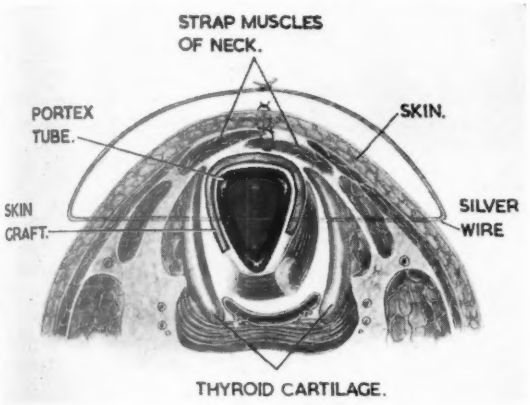
It appeared that the condition of the larynx was initially one of congenital stridor, and that this had been made worse by the probing at the first laryngoscopy. This probably produced submucosal damage to the left side of the larynx, with consequent fibrosis and organic narrowing. Certainly the laryngoscopic appearance was new to me, and did not conform with the various types of abnormality which cause the syndrome of congenital stridor. The Wassermann reaction was negative.

The problem this case presented was of considerable magnitude. If nothing were done, the child would develop without speech, and with a permanent tracheostomy throughout her years of development. On the other hand, any reconstructive operation on the larynx would be much easier at a later date when the field of operation would be so much larger.

If a reconstructive operation were attempted at once, it was realized that it would be a somewhat difficult procedure, but if success were achieved, it would be obviously of great benefit to the child. The hoped-for outcome was for a functioning larynx, with a usable though weak voice and a normal airway, together with closure of the tracheostomy. It was thought that probably the larynx could be made large enough for normal respiration, but whether or not the voice would be restored was unpredictable.

These various points were discussed with the mother, and she agreed that an immediate reconstructive operation should be undertaken. Depending on its outcome, it was intended to close the tracheostomy at a later date. Accordingly, on July 29, 1955, the procedure was embarked upon. Under general anaesthesia a vertical incision was used through the skin and superficial tissues, eventually opening the larynx in the midline. The cricoid cartilage was cut through, and the trachea as far down as the tracheostomy opening. The right true cord was identified, and appeared normal. The left side of the larynx showed no proper structure, and was adherent across the anterior commissure but not in a web formation. The whole of the left side of the larynx was separated in the submucosal layer from the thyroid cartilage and removed, leaving only the cartilaginous surface as the left laryngeal boundary. The right side of the larynx was not interfered with. A No. 1 triangular portex tube (Negus pattern), cut to 2 in. in length, was then inserted in the wound from the cephalad point of the thyroid cartilage to the tracheostomy tube in the trachea; the tube was used with the base placed anteriorly. This was covered on the anterior and lateral aspects with a skin graft of appropriate size, the appearance then being as in the figure. No attempt was made to close the thyroid and cricoid cartilage over this or the trachea. The strap muscles of the neck were closed over the skin graft, and the superficial tissues and skin over these. A silver wire was inserted through the thyroid

cartilage and portex tube to retain the latter in position. An oesophageal tube was placed through the nose for feeding purposes, the tracheostomy tube being still in place. The child stood the procedure well, and was returned to the ward in good condition. She was



nursed for 24 hours in an oxygen tent under constant supervision, with suction as necessary. There was no pyrexia, and feeding presented no difficulty. The child was under full antibiotic therapy.

On August 5, 1955, the portex tube was removed by direct laryngoscopy, the silver wire stay suture having been first withdrawn. The tube came away easily with no adherent skin. The laryngeal aperture appeared adequate, but the tracheostomy tube was not removed.

On August 10, 1955, it was seen that the child was breathing through the nose, so the tracheostomy tube was removed. By August 20, 1955, the tracheal stoma had almost closed. The child made a 'noise' when crying, so that it could be assumed that there was going to be some form of voice. However, on August 30, she contracted an upper respiratory infection. There was a return of laryngeal stridor, and the tracheostomy tube was reintroduced.

On September 8 a direct laryngoscopy was performed. The larynx looked normal on the right side, and posteriorly the inlet was satisfactory. There were a few granulations on the mucosa anteriorly on the left side and these were removed and the laryngeal aperture gently stretched by opening the jaws of a pair of Patterson's forceps in it. On September 20 the tracheostomy tube was removed, and there has been no further trouble since this date.

On October 6 a further direct laryngoscopy and tracheoscopy was performed. The laryngeal aperture was satisfactory and the tracheal lumen adequate and the right true cord was seen to move. The anterior wall of the trachea appeared very injected (this was the area composed of skin graft), but there were no granulations. The tracheostomy orifice had closed spontaneously.

This patient has now returned home and it is hoped that she will shortly catch up in speech with children of her age.

It seems that the risks undertaken in operating on this child at this age were justified by the outcome. The operating field is extremely small, but provided adequate care is taken, the procedure is not particularly difficult. With this patient it may be necessary at a later date to free the skin of the neck from the underlying fibrous tissue, since the original tracheostomy scar was very adherent.

It was interesting to find that the tracheostomy stoma closed spontaneously; this is most unusual in a child so young, and in whom the tracheostomy tube had been in position for one and a half years. Provided that the laryngeal aperture can be made adequate, it seems that this favourable outcome can be expected.

I should like to express my thanks to Mr. Pereira for referring this case to me, to Dr. Sheila Anderson for her skilful anaesthesia on each occasion and to my Registrar, Mr. Halfhide, for his help and encouragement. The care of the sister and nurses in the ward contributed in no small measure to the successful outcome.

KLEBSIELLA PNEUMONIAE (FRIEDLÄNDER'S BACILLUS) INFECTIONS IN INFANCY

BY

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Klebsiella pneumoniae infections are uncommon in premature and maternity units as well as in paediatric wards. Hospital epidemics are exceptional, only some five published reports being known to us. Kliewe (1930) reports an epidemic in which pneumonia developed in 11 or 12 infants in a single ward, *Klebsiella* having been cultured from the pharynx of all 11. Two infants died. Of the remaining 130 children in the institution, only one had a positive throat culture. Jampolis, Howell, Calvin and Leventhal (1932) witnessed an outbreak of diarrhoea in 34 newborn infants caused by *Bacillus mucosus*. There were 14 deaths. Walcher (1946) found *Bacillus mucosus* in 12 cases of infantile diarrhoea. Obrinsky, Dormont, Fowler and Ruhstaller (1950) recorded 10 infantile infections caused by the Friedländer aerogenes group of organisms, with five deaths. Očko-Četkovič and Vesenjak-Zmijanac (1953) report on fulminant pneumonia and grave diarrhoeal disorders caused by *Aerobacter aerogenes* in premature babies and infants.

In our hospital, during the period between December 7, 1953, and July 1, 1954, positive *Klebsiella* cultures were obtained from the pharyngeal swabs of 52 premature babies, newborn babies and infants, of two children and two adults, as well as from the mucopurulent discharge in two children with otitis, and from the cerebrospinal fluid of a newborn infant, altogether on 94 occasions. The organism was often isolated in pure culture or was found to be predominant. The infections were severe, moderate or even mild. Notwithstanding its presence in throat cultures, it proved very often entirely harmless. It may be, however, that a *Klebsiella* population of a purely saprophytic nature assumes pathogenic properties.

Such a high incidence of *Klebsiella pneumoniae* infections seems to be unrecorded as yet in the paediatric literature, and the publication of our material, therefore, may be of some use.

Differentiation of the Escherichiae

In the classification of Bergey (1948) the *Escherichiae* include Genus I, *Escherichia*; Genus II, *Aerobacter* and Genus III, *Klebsiella*. The absence of a capsule permits us in most cases to differentiate *Escherichia coli* from *A. aerogenes* and *Klebsiella pneumoniae*. Because the latter two organisms show a close morphological, cultural, biochemical and antigenic relationship, their differentiation has been abandoned by numerous authors. Obrinsky *et al.*, for instance, use the term '*Friedländer-Aerogenes* infections'.

We, however, do not think that the differentiation of these two micro-organisms should be given up. Even their epidemiological behaviour shows some difference: we have been able to isolate *A. aerogenes* from throat cultures only very rarely and never in succession or in a great number of cases simultaneously, but we did, during our epidemic, isolate *Klebsiella pneumoniae* repeatedly in numerous cases. According to our observations, the *Klebsiella* cultures on blood and blood-chocolate agar are characterized by white or greyish-white, sticky, mucoid and more or less transparent colonies. *A. aerogenes* produces mucoid, sticky, white or greyish but definitely less transparent colonies. Microscopically, *Klebsiella* shows a more uniform and monotonous picture than that of *A. aerogenes*. The *Klebsiella* strains isolated by us have grown well on blood, blood-chocolate and broth-agar, fermented lactose, dextrose, maltose and mannite; they were, however, unable to produce indol. The methyl-red test was negative, the Voges-Proskauer test often positive. There was often an adequate growth in Koser-citrate-medium. But the *A. aerogenes* strains have shown similar behaviour. The best method of distinguishing these two micro-organisms has been the inoculation of white mice: very small quantities of *Klebsiella pneumoniae* killed the mice within 24 hours, whereas the *A. aerogenes*

either did not kill them or did so with a substantial delay. Weiss, Eisenberg, Alexander and Flippin (1954) established their aetiological diagnosis on similar grounds; in 24 out of 383 patients affected with pneumonia, the aetiological role of *Klebsiella pneumoniae* was established by these authors. As our strains have proved lethal to white mice within 24 hours, we shall use the term *Klebsiella pneumoniae* (Friedländer's bacillus) infections in the present paper.

The Route of *Klebsiella pneumoniae* Infection

The latest data show that *Klebsiella pneumoniae* infections in children are on the increase. This may be due either to the greater frequency of this organism or to its greater virulence. The first suggestion is based on the fact that the suppression of penicillin-sensitive Gram-positive organisms by antibiotic therapy is followed by the overgrowth of Gram-negative bacteria, and among them of *Klebsiella pneumoniae*. The observations made by Wilhelm and Orkin (1949), on the other hand, lend support to the other view, since the higher incidence of grave urinary tract infections caused by *A. aerogenes* as observed by these authors might be ascribed to an increased virulence. Neither Obrinsky *et al.* (1950) nor Weiss *et al.* (1954) were able to determine whether they faced a real or apparent increase in infections.

The epidemic described by Kliewe (1930) and Jampolis *et al.* (1932) suggests that the high incidence of *Klebsiella* infections may be unconnected with antibiotic treatment. The infection may spread by carriage even when no antibiotic treatment has been given. We found in our epidemic that in many cases the throat swabs were positive before any antibiotics were given. It was not at all exceptional to find that *Klebsiella pneumoniae* disappeared spontaneously from the throat cultures before the start of antibiotic therapy. We have had cases where serial throat swabs yielded alternately positive and negative cultures. The question whether the epidemic had anything to do with local circumstances was also pertinent. Valuable evidence could be gathered from our premature unit. Premature babies born outside our hospital are rarely admitted. Therefore, it was very important in view of the above problem that *Klebsiella pneumoniae* could be recovered from the throat swabs of two premature babies admitted from two widely separated districts of Budapest. This fact appears to indicate that we were actually faced with a town rather than a local increase in the numbers of this organism.

A case (Steiner, 1954) of *Klebsiella pneumoniae* meningitis in a newborn baby was the first appearance of this organism in our unit. The second infection occurred only two and a half months later. Infection and disease in the newborn might originate directly from the mother or from the immediate environment. Maternal infection may take place during intra-uterine life, during parturition and after birth. As the infant was isolated from the mother immediately after birth, the latter possibility may be excluded. Attempts at isolating *Klebsiella pneumoniae* from the throat or genital organs of the mother failed. Thus, a maternal source of infection was highly improbable. *Klebsiella pneumoniae* could not be isolated either from the throats of premature infants sharing the same ward or from those of newborn babies staying at the same time in the maternity unit. Nor could this agent be grown from the air of these wards or from the throat swabs taken from the nurses in contact with the baby. Unfortunately, no investigations in faeces were carried out. Since the newborn baby had been given penicillin for four days before having been taken ill with meningitis, it was suggested that this therapy might have played a part in the development of *Klebsiella pneumoniae* meningitis.

Our observations seem to suggest that the higher incidence of diseases due to *Klebsiella pneumoniae* (and to other facultatively pathogenic Gram-negative organisms) has not yet been adequately explained. Since it has been demonstrated that *Klebsiella pneumoniae* could be recovered in a great number of premature babies who had received no antibiotic treatment and that local causes could not be detected, it must be assumed that the number of *Klebsiella pneumoniae* organisms is on the increase. If antibiotic therapy is supposed to play an essential part in this increase, we cannot say that the observations gathered during our epidemic have given much support to this suggestion. In our unit, the epidemic caused by *Klebsiella pneumoniae* was of sudden onset and it came to a sudden end. The first case appeared on December 7, 1953. Until February 16, 1954, we saw no further case. Throat cultures were positive in March on 27 occasions, in April on 25, in May on 27 and in June on 11; in July and September now and then on one occasion (altogether 94 times). Since the same principles of antibiotic therapy were observed in our unit long before the outbreak of the epidemic and have been followed ever since, we do not believe that antibiotic treatment was responsible for the outbreak of the epidemic or that it has fostered it in any way. Thus, our observations, without giving

a definite answer to the question of how *Klebsiella pneumoniae* led to this epidemic, do give, however, an important indication: the infections caused by *Klebsiella pneumoniae* and other uncommon pathogens are not simply the consequence of antibiotic therapy.

The Pathogenic Role of *Klebsiella pneumoniae*

The pathogenic role of *Klebsiella pneumoniae* seems to be different in children and in adults. *Klebsiella* are a group of encapsulated Gram-negative bacilli, present in the normal flora of the mouth and in the respiratory and intestinal tracts in adults (Beeson, 1954). Therefore, in healthy individuals, they are not thought to assume pathogenic properties. On the other hand, Bloomfield (1921) dwells on the fact that the bacillus is rarely found in the upper air passages of healthy individuals. This is confirmed by the investigations of Weiss *et al.* (1954). According to Julianelle (1930) and Henriksen (1952), 40 out of the 42 strains 'A' of *Klebsiella pneumoniae* came from human sources. From these 40 serological types, 33 were causative of pneumonia, one of liver abscess, five were saprophytes of the respiratory tract and one was cultured from the urinary tract. From 12 strains of Type B, seven were cultured from animals, the others from human sources (pneumonia, throat, liver abscess, faeces). Type C is very rare, three strains having been isolated from human pneumonia, one from paranasal sinuses and one from the nose. Both the above-mentioned authors conclude that Types A and C are highly pathogenic for man, especially Type A, which is generally the cause of *Klebsiella* pneumonia. According to Weiss *et al.* (1954) Type A was causative only in three out of 24 cases of *Klebsiella pneumoniae* infection. As regards its occurrence in children, less than 30 cases of acute Friedländer pneumonia have been reported up to 1950 (Obrinsky *et al.*, 1950). Even during hospital epidemics it was most exceptional to find this organism in the throat of healthy children (Kliewe, 1930). For this reason, positive throat swabs or sputa may induce the paediatrician to ascribe the actual illness to this agent, and his therapeutic measures will also be guided by this belief. We have found it sometimes very difficult to say whether a positive *Klebsiella pneumoniae* throat culture had anything to do with the actual illness during the time of an epidemic. We had cases in which a pulmonary infection was present and the nasopharyngeal or laryngeal swabs yielded pure or almost pure growths of *Klebsiella pneumoniae*, which, however, were not causative. In one of our premature infants the clinical diagnosis of interstitial pneumonia could be made in spite of a positive throat culture. The necropsy confirmed this diagnosis without revealing any sign of *Klebsiella pneumoniae* infection. In another case, clinical diagnosis pointed to aspiration pneumonia (the bacteriological finding in the throat culture revealed *Klebsiella pneumoniae*) and as soon as a sunflower seed was removed with the aid of the bronchoscope the child recovered completely.

These observations raise the following questions: When is *Klebsiella pneumoniae* to be regarded as causative and when as a mere saprophyte? Are there carriers of *Klebsiella pneumoniae* among infants? Which is of greater aetiological significance, if *Klebsiella pneumoniae* is isolated from nasopharyngeal swabs in pure growth, or if it is only predominant? What is the significance of small numbers of *Klebsiella pneumoniae* in nasopharyngeal cultures?

It is certainly not easy to find an answer to these questions, but clinical experience may be of great assistance. Thus, Adams (1952) points out that primary pneumonia of bacterial origin is rare in early infancy, whereas primary pneumonia supposed to be of viral aetiology is characteristic of this age, premature infants being particularly susceptible. Our own experience confirms that many cases of *Klebsiella* pneumonia may be overlooked if only organisms involving destruction or abscess formation are taken into account. The results of experimental investigations do not recommend us to attach too much value to the presence of bacteria in throat cultures. Blake and Cecil (1920) demonstrated in animal experiments that pure cultures of *Streptococcus haemolyticus* and *Diplococcus pneumoniae* never cause pneumonia unless introduced by the intratracheal route, whereas influenza bacilli were capable of initiating infection by mere nasal inoculation. According to Robertson (1943), the presence of infected exudate in the upper respiratory tract is harmless to the lungs; only when passing the epiglottic barrier does it lead to pulmonary infection. In the case of droplet infection, the agent must reach the terminal airways in large numbers, without the possibility of being eliminated, in order to develop pneumonia. Bacterial pneumonia is preceded, as a rule, by some disorder of the respiratory passages.

In some cases it is easy to ascertain whether *Klebsiella pneumoniae* has been causative or merely a saprophyte. For instance, in the case of a premature infant weighing 2,000 g., pure cultures of *Klebsiella pneumoniae* were obtained from the nasopharynx on the tenth day of its stay in our unit, though the weight curve showed a steep rise and its condition was excellent. *Klebsiella pneumoniae*

disappeared from the throat without any treatment. Clearly the organism is not necessarily pathogenic in prematures. This premature baby was a carrier. This observation having been confirmed on other premature and newborn babies, we do not believe that healthy carriers of *Klebsiella pneumoniae* require any preventive treatment.

In other cases our task was more difficult. For instance, *Klebsiella pneumoniae* and Gram-positive cocci could be grown from the throat of a newborn baby weighing 2,820 g. Persistent vomiting for over five days was remarkable. We wondered whether *Klebsiella pneumoniae* could be held responsible for it, but this proved not to be the case, since the vomiting still continued when the nasopharyngeal cultures no longer contained *Klebsiella pneumoniae* and Gram-positive cocci or Gram-negative bacilli only in small numbers.

A premature baby weighing 1,500 g. was thriving satisfactorily, having gained 500 g. within a month. When the baby was 5 weeks old, a routine examination revealed haemolytic streptococci, Gram-positive cocci and diplococci but no *Klebsiella pneumoniae* in nasopharyngeal cultures. Three days later a temperature of 38° C., with rapid breathing and harsh respiration had developed. Penicillin induced apyrexia in 24 hours and the development of the infant remained undisturbed. At the date of the onset of temperature *Klebsiella pneumoniae* could be grown in pure culture from the nasopharyngeal swab. Though this bacterium is insensitive to penicillin, it could no longer be demonstrated after treatment. Since the patient recovered as a result of penicillin treatment, and *Klebsiella pneumoniae*, which is known to be unresponsive to penicillin, disappeared from the throat during treatment, we do not believe that in this case *Klebsiella pneumoniae* played any part as an infecting agent.

A 1-day-old premature baby was *Klebsiella* positive without presenting any symptoms when admitted to our unit. A few days later pneumonia developed and the patient was started on penicillin. Twenty-four hours later the throat culture yielded, apart from a few Gram-positive cocci, *Klebsiella pneumoniae*. On the basis of this finding, streptomycin was substituted for penicillin. A 10 days' course of treatment resulted in complete cure. However, three weeks later the throat cultures were again *Klebsiella*-positive. Now dyspepsia developed but it responded to streptomycin and threomycin. Thus, in this case positive *Klebsiella pneumoniae* cultures were accompanied by pneumonia, dyspepsia and perfect condition and development. Whereas the aetiological role of *Klebsiella pneumoniae* is probable, it does not conclusively cause dyspepsia. The patient might have been only a carrier of bacilli at the time when his development was satisfactory.

Our experience favours the view that *Klebsiella pneumoniae* in the throat even of the youngest baby has not necessarily pathological consequences. In each individual case it must be decided whether we are faced with the causative agent or whether we have to deal with carriers only. In our ample material we have met numerous carriers. The question whether there is any connexion between *Klebsiella pneumoniae* demonstrated in the nasopharynx and the actual illness must be raised in each individual case, in particular during epidemics. *Klebsiella pneumoniae* obtained in pure growth may have a greater aetiological significance than in cases where it is but a member of the nasopharyngeal flora. But here we must state clearly that, in our opinion, *Klebsiella pneumoniae* in the nasopharynx, whether in pure culture or only as the predominant organism, is by no means indicative of any connexion existing between the actual illness and this agent. Thus, statements to be found in textbooks (Nelson, 1954), according to which a bacteriological finding is diagnostic of *Klebsiella* pneumonia, need revision.

In case of mixed bacterial cultures, it would have been necessary to separate them from one another and to carry out sensitivity tests separately with each. However, even with this procedure we would not have been able to decide in each individual case which of the various strains were responsible for the symptoms observed. Whereas formerly the simultaneous aetiological role of several agents in bronchopneumonia was generally acknowledged, to-day it is, on the contrary, believed that even if several organisms are found it is only one of them which causes the disease (Adams, 1952). In cases where a mixed culture is found, the role of *Klebsiella pneumoniae* would be ascertained, apart from the clinical course, by the presence of Types 1-6 of groups A or C but mostly by the demonstration of specific antibodies in the patient's serum.

The observations according to which the epidemic described by Kliewe (1930) was confined to pneumonia cases and that witnessed by Jampolis *et al.* (1932) to diarrhoeal cases, directs our attention to the problem of typing *Klebsiella pneumoniae*. Unfortunately, it is rather difficult to separate the different types of *Klebsiella pneumoniae*, of which more than 50 are known to-day, not only because there are no specific antisera available, but also because capsulated bacilli are not easy to agglutinate. According to Grotts (1949) there are types of Friedländer bacilli which are agglutinable and others which are not. The serological difficulties are

clearly shown by the investigations of Henriksen (1952). Only 141 out of 189 capsulated strains responded to the antisera of generally known types, but the typing was possible in 90 strains (47·6%) only; in 46·1% this was not feasible with 61 type-sera.

In our opinion, the actual state of knowledge does not allow us to consider the causal role of *Klebsiella pneumoniae* in children as proven unless (1) this organism is cultured from blood or from pleural effusion, (2) demonstrated in a cerebrospinal fluid which shows inflammatory symptoms, (3) grown from urine taken under sterile precautions and the number of white blood cells in the urine is increased, (4) demonstrated in the faeces during a dysentery epidemic among children, and the carrier or carriers of *Klebsiella pneumoniae* having been removed, the epidemic comes to an end, and (5) the significance of a positive nasopharyngeal culture of *Klebsiella pneumoniae* in the diagnosis of *Klebsiella* pneumonia is different when we are faced with an isolated case or with a mass infection. This problem will be discussed in another report (Steiner, in the press).

Summary

An outbreak of infection *Klebsiella pneumoniae* in infants is described. Antibiotic therapy did not seem to play any part. In the course of an epidemic the fact that *Klebsiella pneumoniae* is only a facultative organism must be taken into account. It should be considered in each case whether the presence of *Klebsiella pneumoniae* in the nasopharynx is in any way connected with the actual disease. In the differential diagnosis of sepsis, meningitis, diseases of the urinary tract and pneumonia the aetiological role of *Klebsiella pneumoniae* has to be considered as being more frequent than before.

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ACUTE GLOMERULONEPHRITIS IN INFANCY*

BY

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Karsner (1908) described 'congenital nephritis' in an infant who died 45 minutes after a normal birth, and Lapage (1932) discussed acute haemorrhagic nephritis in an 11-day-old boy who died in a few days. Conrad (1938) gave a résumé of three infants with neonatal nephritis for which no cause was found. One infant died on the seventh day of life, but the others recovered. Generalized oedema, haematuria and albuminuria were common to all. The Kahn test was negative in one infant. Their births were normal and the ante-partum history of the mothers was uneventful. Acute glomerulonephritis in babies under 2 years old has been described. Smith (1946) reported acute glomerulonephritis, Wilms tumour and a horseshoe kidney in a 10-month-old boy and Blechmann (1950) described acute glomerulonephritis with uraemia in a 21-month-old baby, who made a complete recovery.

Various attempts have been made to analyse and classify nephritis in children. Wyllie and Moncrieff (1926) analysed 87 cases of juvenile nephritis in children between the ages of 2 and 10 years and divided them broadly into three groups: (1) acute haemorrhagic nephritis (22 cases with no deaths); (2) acute exudative nephritis (23 cases with six deaths); (3) chronic nephritis (42 cases with 12 deaths).

Aldrich (1930, 1931) examined 186 consecutive children with nephritis and placed them into three main groups. A subsidiary group included cases of subacute bacterial endocarditis, syphilis, tuberculosis and renal infantilism. Aldrich's groups are: (1) acute post-infective haemorrhagic nephritis (129 cases, 6·2% died); (2) chronic non-specific nephritis (24 cases, 54·2% died); (3) nephrosis (20 cases, 35% died); (4) other cases (13 cases, 4·6% died). The ages of the children were not mentioned. Rennie (1934) reviewed acute nephritis in 10 infants under 18 months old; five of them were below 1 year old, the youngest 4 months old. There were seven deaths. No definite cause was found and syphilis was not a factor.

Guthrie (1936) studied nephritis in 46 children under 11 years of age, the youngest child being 15 weeks old. He noted that the acute types of nephritis predominated in children, in whom the renal lesion was usually mild and was rarely complicated by arterial disease. Burke and Ross (1947) reviewed 90 consecutive cases of acute glomerulonephritis in children between the ages of 4 months and 10 years. The commonest presenting symptoms were oedema (59·9%), gross haematuria (25·5%), abdominal pain (6·7%) and other symptoms, included vomiting, convulsions, dyspnoea and dysuria. Anaemia was a frequent finding.

The cause of nephritis is still not definitely known. There seems to be a relationship between acute glomerulonephritis in children and young adults and a preceding streptococcal infection. Dingle, Rammelkamp and Wannamaker (1953) and Wilmers, Cunliffe and Williams (1954) have identified most of the infections with group A haemolytic streptococcus type 12.

Yampolsky and Mullins (1945) described acute glomerulonephritis in a 2-month-old infant with congenital syphilis. This paper is a classical example of syphilis as a cause of glomerulonephritis in early infancy. Murray and Calman (1953) demonstrated that antibodies circulated in the foetal blood from birth, and these findings are important in any discussion on the cause of nephritis which is based on an antigen-antibody reaction. Brambell, Brierley, Halliday and Hemmings (1954) made several important observations on the transference of passive immunity from the mother to her young.

Bernheim and Gaillard (1951) described two important presenting features of acute nephritis in infancy: (*a*) the urinary syndrome, in which red cells and casts were found in the urine; and (*b*) the mimicry of other conditions, especially acute haemolytic anaemia, acute leukaemia and cardiac disease.

* The subject matter formed part of a thesis for the degree of M.D. of the University of Cambridge.

Bernheim (1952) distinguished five main clinical types of acute nephritis in children, *viz.*, eclamptic, anuric, anaemic, cardio-pulmonary and nephritis with a neurotoxic syndrome. Ultimate prognosis should always be very guarded. These last two papers show the difficulty of diagnosis of nephritis in infancy due to its variable forms of presentation.

Doxiadis, Goldfinch and Cole (1952) have disproved some earlier work that 'proteinuria' was a normal physiological finding in infants during the first week of life.

In reviewing the literature it is clear that nephritis in children is usually a mild condition with ultimate recovery. There is often a history of an antecedent upper respiratory tract infection. No classification of the causes of nephritis in children under 1 year old could be found. The mention of a familial or hereditary factor in nephritis at any age is most uncommon. A study is presented here of two fatal cases of acute glomerulonephritis in members of the same family.

Case Reports

Case 1. The first child, a girl, was born on September 6, 1950. She was three weeks overdue and weighed 5 lb. 15 oz. at birth. The baby was normal after a spontaneous delivery following a trial labour. She was breast-fed for six weeks and then was weaned on to National dried milk due to the failure of lactation. During her last month of life, she had been having additional broths and sieved vegetables. She had never been given any teething powders and had had no previous illnesses. On February 20, 1951, she had a primary vaccination with a normal reaction.

The mother had been well throughout the antenatal period and there was no relevant family history.

On February 27, 1951, the baby was brought for examination because she had been vomiting and had passed some dark stools and urine. Ten days earlier the mother had noticed that her baby was not taking her usual quantity of feeds, *i.e.*, 3 oz. instead of 5 oz. At this time she had vomited once. Three days before examination the grandmother noticed that the baby was passing dark-coloured urine.

On examination, the infant, aged 5 months 3 weeks, weighed 17 lb. 4 oz., temperature (rectal) 100° F., pulse 200/minute, respirations 18/minute. The face and mucous membranes were strikingly pale. No oedema, petechiae or purpuric spots were present. The anterior fontanelle was slightly depressed. The examination of the sclerotics, ears, throat, neck, heart, lungs and nervous system was normal. The abdomen was not distended and the liver and spleen were not felt. No enlarged lymph nodes were palpable in the neck, axillae or groins. The urine was dark red and contained much albumin and many red blood cells.

Clinical Course and Treatment. The baby was admitted to the cottage hospital on February 27 with vomiting, and was given one-fifth normal saline by mouth.

On February 28 she was still a very pale infant, and retained no fluids given by mouth. She was given one-fifth normal saline subcutaneously.

Her blood group was ORh positive, and a blood count gave: red cells 1·82 m. per c.mm., Hb 33% (haemoglobin standard, Hb 100% = 14·8 g. %); white cells 10,600 per c.mm. (polymorphs 60%, lymphocytes 35%, monocytes 4·5%); few platelets. Urobilinogen was not increased.

On March 1 the baby was transferred to a general hospital. She was a very ill, dehydrated baby with pale grey lips. Her temperature was 101·8° F. A little 'dextrimaltose' was taken by mouth. The blood urea level was 268 mg. %. A blood transfusion of 120 ml. packed cells was given. On March 2 the blood urea was 238 mg. %, Hb 53% and the infant's colour had improved. On March 5 the red cells numbered 940,000 per c.mm., with nucleated red cells 24 normoblasts per 200 white cells. White cells numbered 10,000 per c.mm. (polymorphs 47%, lymphocytes 51%, monocytes 2%).

On March 6 the infant vomited three times, the vomit containing some altered blood, and a transfusion of 165 ml. packed cells was given. On March 8 the blood urea level was 336 mg.% and Hb 64%, the latter decreasing on March 10 to 60% and on March 13 to 42%. On March 14 the blood urea level was 392 mg. %, and a transfusion of 95 ml. packed cells was given. On March 15 the red cells numbered 3·76 m. per c.mm. Hb 76%, white cells 10,000 per c.mm. (polymorphs 68%, lymphocytes 31%, monocytes 1%), blood urea 442 mg. %, and on March 16 red cells 3·5 m. per c.mm., Hb 68%, platelets 177,000 per c.mm., blood urea 532 mg. %, and on March 19 blood urea was 650 mg. %, when a transfusion of 120 ml. packed cells was given.

On March 20 the infant was cyanotic with fixed, dilated pupils and had been vomiting altered blood. She died at 6.30 p.m.

Necropsy. A necropsy was made on March 21, 1951. The body was that of a female infant of good physique with a pale and waxy-looking skin. No cutaneous haemorrhages were seen. There was slight oedema of the legs.

The brain was normal. The superior longitudinal sinus had not been injured by the fontanelle transfusions. The heart was normal in size, and its muscle was pale. There was no congenital abnormality. The lungs were well expanded and were a normal bright red. There was no pneumonia. A small amount of altered blood, mixed with bile, was found in the stomach. The liver showed several haemorrhagic spots on the peritoneal surface but the cut surface was normal. The spleen was firm in consistency and its cut surface appeared to be rather dark.

Both kidneys were slightly enlarged, dark red and showed some loss of definition between the cortex and the medulla. The capsule stripped easily, leaving a smooth mottled surface which was free from haemorrhage. A few small white triangular areas were present in the cortex. The renal veins were not thrombosed and

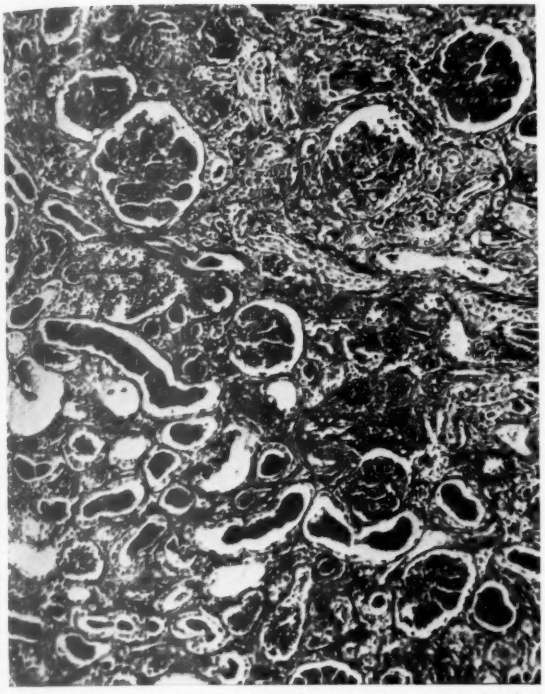

FIG. 1.—Variation in size of glomeruli; dilated convoluted tubules filled with coagulated eosinophilic material (haematoxylin and eosin × 60). *Infant 1.*

the renal pelves were free from haemorrhages. No congenital abnormalities were found in the renal tract.

The bladder contained a small amount of turbid material, which gave a heavy culture of *E. coli*.

HISTOLOGY. The liver showed the presence of free iron and the sinusoids were slightly dilated. The spleen was normal except for excess free iron.

In both kidneys the renal capsule was not thickened and the aglomerular subcapsular zone was absent, though this might have been due to the age of the baby.

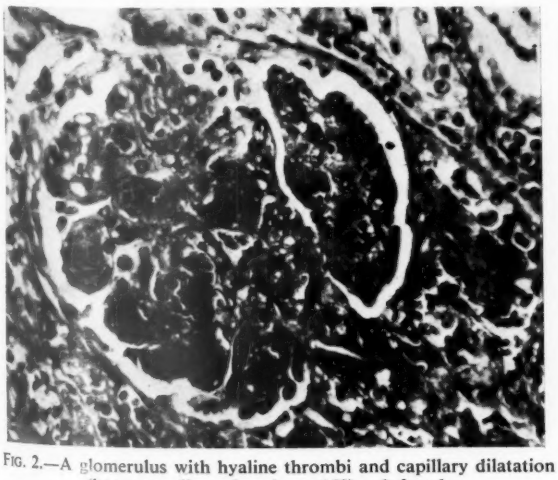

FIG. 2.—A glomerulus with hyaline thrombi and capillary dilatation (haematoxylin and eosin × 160). *Infant 1.*

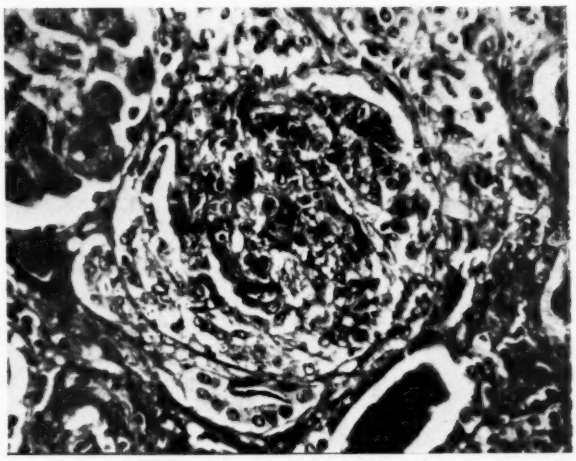

FIG. 3.—A glomerulus with early crescent formation (haematoxylin and eosin × 160). *Infant 1.*

The glomeruli were variable in size (Fig. 1). Approximately half of them were normal, the others showed certain changes, which varied very much in degree. Many showed a pronounced capillary dilatation with hyaline thrombosis (Fig. 2), and in some there were small infiltrations with polymorphonuclear cells. The glomerular tufts were distorted and adhesions appeared between the tufts and Bowman's capsule. Proliferation of Bowman's capsule was seen and this had led to definite crescent formation (Fig. 3).

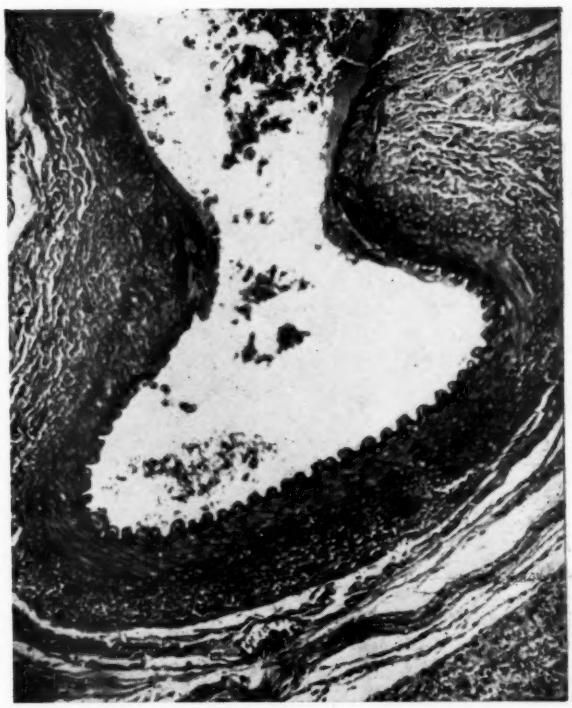

FIG. 4.—A large arteriole in which there is no pathological change (haematoxylin and eosin × 60). *Infant 1.*

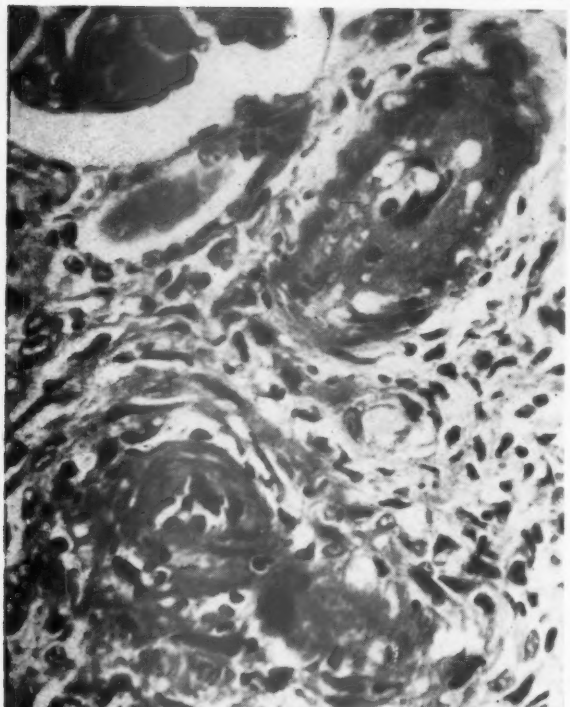

FIG. 5.—Three small afferent arterioles with fibrinoid necrosis (haematoxylin and eosin × 310). *Infant 1.*

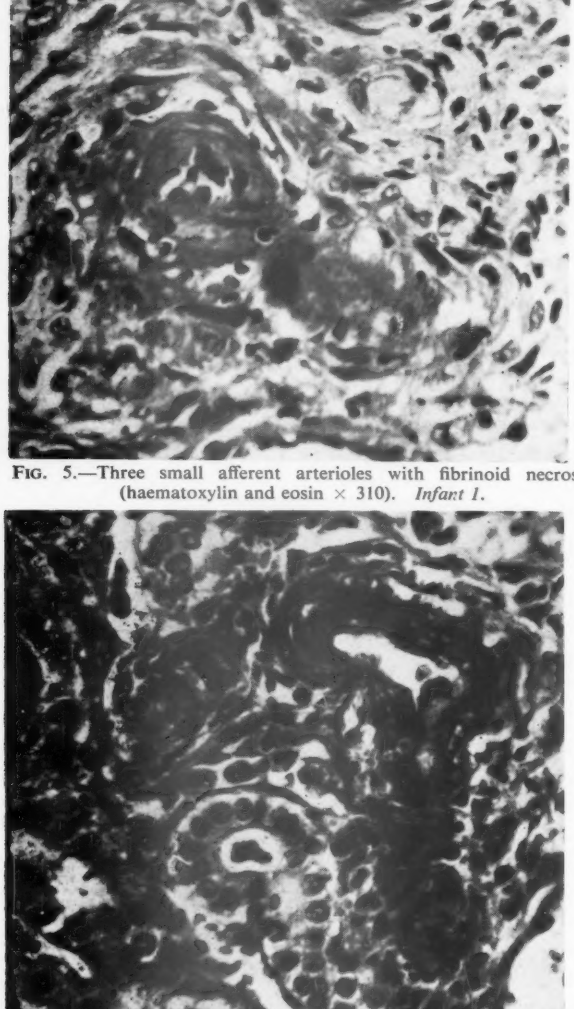

FIG. 6.—An afferent arteriole with fibrinoid necrosis (tangential cut) (haematoxylin and eosin × 310). *Infant 1.*

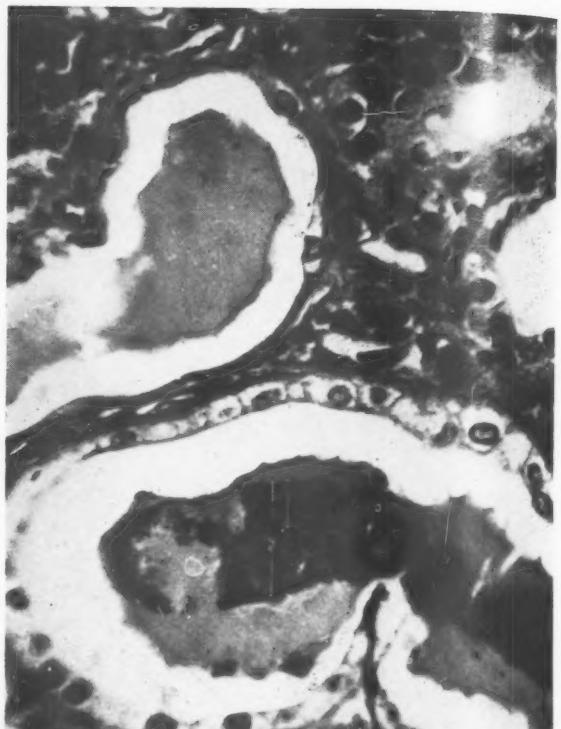

FIG. 7.—Convoluted tubules with 'casts' of eosinophilic material, which were a very prominent feature of this kidney (haematoxylin and eosin × 320). *Infant 1.*

The medium- and large-sized arterioles were normal (Fig. 4). A generalized capillary dilatation was present throughout the kidney. Some of the afferent glomerular arterioles showed fibrinoid necrosis, which in some instances had completely filled the lumen of the blood vessels (Figs. 5 and 6).

A generalized tubular dilatation was present, which affected in particular the proximal convoluted tubules. A special feature of this lesion was the presence of amorphous eosinophilic (presumably) proteinous material, which filled the dilated tubules (Fig. 7).

The interstitial tissue was slightly increased and was oedematous. No inflammatory changes were seen in the renal pelvis.

The lesion was considered to be an acute glomerulonephritis, which was already passing into the subacute phase.

Case 2. The second child, a boy, was born on December 20, 1951. He was 17 days overdue and weighed 6 lb. 14½ oz. at birth. Signs of foetal distress were present just before spontaneous delivery. The baby was born in a state of white asphyxia, but soon recovered. He was breast-fed for six weeks and then weaned on to National dried milk due to the failure of

lactation. During the past two weeks, the baby had also been given rusks. He had had no previous illnesses and had not been vaccinated. The mother had been well throughout the antenatal period.

On May 20, 1952, the baby was seen because of his pallor and the blood-stained urine. On the previous day the mother thought that her baby looked pale. He had had four loose, orange-coloured stools. He was given one teething powder, which contained approximately 0·4 grain of calomel. Overnight the napkins were stained red.

On examination, the baby, aged 5 months, weighed 17 lb. 8 oz., temperature (rectal) 100·2° F., pulse 144 per minute, respirations 36 per minute. He was a vigorous, plump baby with a pale, lemon-coloured skin. The mucous membranes showed a fair colour. The tongue was clean and moist. There were no teeth. The tonsils looked a little enlarged and red. A few purpuric spots were present in both supraclavicular fossae and in the right groin. On examination, the heart, lungs and central nervous system were normal. The abdomen was normal; the liver and spleen were not palpable. There was no oedema. The urine was smoky red and contained much albumin and many red blood cells. The baby was immediately admitted to a general hospital.

CLINICAL COURSE AND TREATMENT. On May 20 Hb was 60%, white cells 12,000 per c.mm. (polymorphs 60%, lymphocytes 36%, monocytes 4%). The platelets were scanty. An occasional smear cell was present but there were no changes in the white cells to suggest a leukaemic condition. The blood group was A Rh positive. The direct Coombs test was negative. The urine contained 2% protein and numerous blood cells, and culture yielded a strong growth of *E. coli*.

On May 21 the blood urea level was 216 mg. %, Hb 42%, and a transfusion of 100 ml. packed cells was given. On May 22 the blood urea was 254 mg. %, Hb 58%, and the baby was more lively and had a better colour. The urine was less bloodstained.

On May 23 the blood urea level was 234 mg. %, Hb 49%, reticulocyte count 6·5%, and a transfusion of 115 ml. packed cells was given. On May 24 blood urea was 230 mg. %, and on May 25 there was a general clinical improvement. The purpura was fading. On May 26 the blood urea was 164 mg. %, Hb 74%, and they had fallen to 144 mg. % and 44% respectively by May 28. The Wassermann and Kahn tests were negative. On May 29 the blood urea level was 124 mg. %, Hb 44%, and a transfusion of 120 ml. packed cells was given. There seemed to be a general clinical improvement, though the baby was still very pale. The haemoglobin level fell less rapidly. The urine was still smoky. By May 30 the blood urea level had risen to 126 mg. % and Hb was 82%.

On June 2 the baby seemed well, except for occasionally vomiting feeds. There was no purpura. The urine was less smoky.

On June 3 the blood urea level was 150 mg. % and Hb 52%. The baby looked very pale. Blood pressure was 104/50 mm. Hg. Two small purpuric spots were seen on the anterior surface of the left forearm and one spot on each ischial tuberosity.

On June 4 the blood urea was 148 mg. %, and on June 5 there was progressive anaemia, but otherwise the clinical condition was unchanged. The urine was a little more smoky.

On June 6, when the blood urea level was 200 mg. %, a transfusion of 100 ml. packed cells was given.

On June 7 the blood urea level was 161 mg. %, Hb 74%, and the baby was ill-tempered and his pallor was increasing. The feeds had been reduced to half-strength. The bowels were opened four times. The urine was moderately bloodstained. On June 8 the baby was very pale, but no oedema was found. Blood pressure was 132/80 mm. Hg. On June 9 the blood urea level was 236 mg. % and Hb 50%. On June 10 the condition was worse. There was slight oedema around the eyes. Five semi-solid, brownish yellow stools were passed. On June 11 blood urea was 280 mg. %, Hb 36%, and the baby was restless and cross. He vomited all feeds. He died suddenly at noon.

NECROPSY. A necropsy was held on June 12, 1952, when the body was that of a pallid, well nourished and normally developed male infant, with several fontanelle venepuncture marks.

The brain was oedematous, but no haemorrhage or any sign of inflammation was found. The meninges were not thickened and there was no haematoma in the longitudinal sinus.

The heart was normal in size and development. The ductus arteriosus and foramen ovale were closed. The lungs were oedematous, but otherwise were normal. The alimentary tract was normal. The liver was congested. The thyroid, thymus and adrenal glands were normal.

The kidneys were enlarged and pale and their cut surface showed a mottled pattern.

The bladder appeared to be normal. No congenital abnormalities were found in the renal tract.

HISTOLOGY. The liver showed a pronounced degree of central fatty change, of the type which is commonly seen in chronic venous congestion. Free iron was demonstrated in the liver sections. The spleen showed much blood pigment and a moderate excess of free iron.

Both kidneys showed similar lesions. The capsule was not thickened and no subcapsular aglomerular zone was present.

The Glomeruli. Most of them showed pronounced histological changes and only a few of them were spared. The affected glomeruli were swollen to two or three times their normal size (Fig. 8). Some glomerular tufts showed great capillary dilatation and there was a small amount of hyaline capillary thrombosis in them. In other tufts all the capillaries were completely thrombosed and contained a variable number of red blood cells, which were beginning to lose their definition (Fig. 9). Many of the swollen glomeruli showed adhesions to Bowman's capsule. Both early and fully developed crescent formation were seen (Figs. 10 and 11).

The Blood Vessels. Some of the afferent glomerular

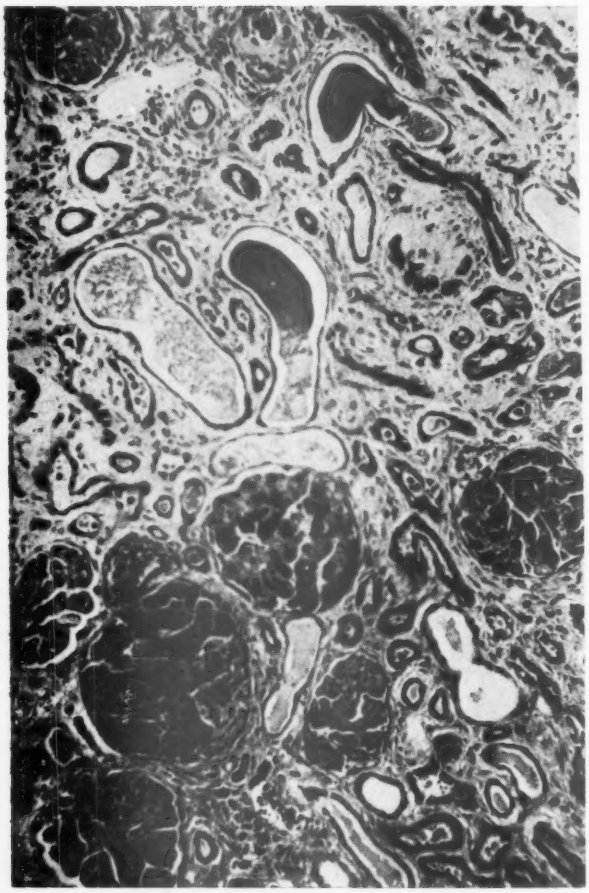

FIG. 8.—Capillary congestion, glomerular swelling and tubular dilatation (haematoxylin and eosin × 80). *Infant 2.*

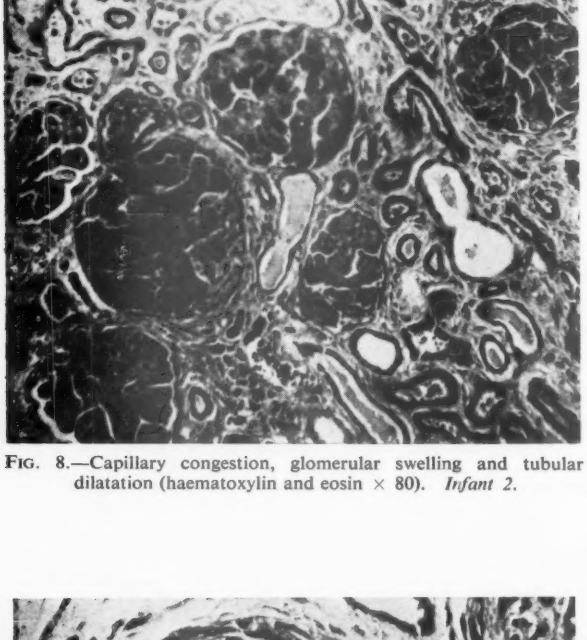

FIG. 9.—A swollen glomerulus with fully developed hyaline thrombi (haematoxylin and eosin × 160). *Infant 2.*

FIG. 10.—A glomerulus with crescent formation (haematoxylin and eosin × 160). *Infant 2.*

vessels showed hyaline necrosis. Other arterioles showed an attempt at recanalization of the blocked lumen.

The Tubules. A generalized tubular dilatation was present, some tubules containing amorphous eosinophilic proteinous material. Other tubules contained fresh blood, altered blood or broken-down red blood cells (Fig. 8).

The interstitial tissue was oedematous and showed signs of early fibrosis.

All these changes were consistent with an acute glomerulonephritis which was passing into the subacute stage. In a comparison of Cases 1 and 2, the lesions appeared to be similar. However, it seemed that the lesion in Case 2 was an older one, for the glomerular lesions were more widespread with fewer normal glomeruli and the crescent formation was much more advanced.

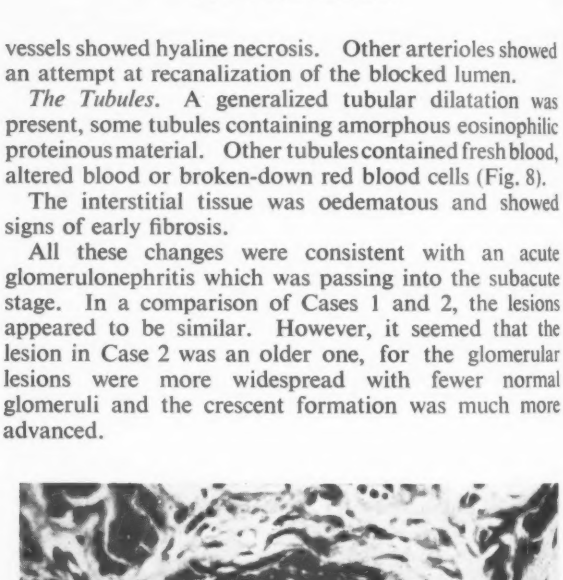

FIG. 11.—A glomerulus with a well formed epithelial crescent (haematoxylin and eosin × 150). *Infant 2.*

Discussion

Familial Tendency in Nephritis. A familial tendency to nephritis is rarely reported (Eason, Smith and Buchanan, 1924; Hurst, 1923). Ernstene and Robb (1931) report a familial epidemic of acute diffuse non-scarlatinal glomerulonephritis in children. Other references include the following: Dickinson (1875), 11 cases of albuminuria in three generations; Kidd (1882), 10 cases of Bright's disease in three generations; Benson (1893), four cases of acute nephritis in four years in one family; Pel (1899), 19 cases of nephritis in three generations; Attlee (1901), three sisters with haematuria and albuminuria; Fergusson (1910), 10 cases of albuminuria; Thomson and Macauley (1920), four cases of acute post-influenzal nephritis in one family. Although familial cases of nephritis have been described, no cases in infancy have yet been found.

Heredity. Heredity may play some part in the cause of nephritis. Hoobler (1924) notes:

> 'The mother with eclampsia may give birth to an infant with diseased kidneys; or the children of such mothers, though born healthy, may have an inherent susceptibility to renal disease.'

Herrick (1909) states:

> 'There can be no question that the tendency to nephritis is at times transmitted. This is often a hereditary arteriosclerotic tendency, the kidney sharing in the general vascular change. The chronic forms may even appear in childhood.'

Zuelzer, Kurnitz and Charles (1951) remark on the frequency of renal vascular disease in the newborn, but do not agree that acute glomerulonephritis in infants is rare. They quote cases of renal cortical necrosis, acute glomerular thrombosis, thrombosis of the renal veins and acute haemorrhagic renal infarction.

Biochemical and Clinical Features in Both Cases. All the blood estimations were done on samples obtained by skin punctures of the heel.

Profound anaemia was a notable feature and the lowest haemoglobin levels were respectively 33% and 42%. The anaemia was normochromic and was believed to be the result of the severe renal damage. The histology showed that the primary lesion arose in the glomerulus and afferent glomerular arteriole. In both cases it was remarkable to see how quickly the haemoglobin level dropped in spite of repeated blood transfusion. The reason for this rapid fall has not been explained. It is appreciated that primary blood diseases may lead to secondary renal damage.

The cause of anaemia in renal failure may be due to blood destruction, blood loss in the urine, or diminished blood formation due to a toxic action on the bone marrow. Platt (1952) suggests that the anaemia of renal failure may be a process of adaptation, since the renal blood flow is limited in quantity.

High blood urea levels in both infants were notable findings from the start of their clinical illnesses. On the second day in hospital the blood urea figures were respectively 268 mg. % and 216 mg. %. In Case 1 the blood urea level dropped to 238 mg. % on the third day, then the uraemia became progressively worse until the blood urea was 650 mg. % on the day before death. The levels in Case 2 were variable; at first there was a steep fall (the lowest figure was 124 mg. % on the tenth day), thereafter the blood urea began to rise until it was 280 mg. % on the day of death.

Blechmann (1950) quotes high blood urea levels in a case of acute glomerulonephritis with uraemia in a 21-month-old baby. The blood urea at the onset of the disease was 40 mg. %; it rose to a maximum figure of 277 mg. % and then settled to 16 mg. % on discharge from hospital.

In both infants the cause of death was uraemia due to acute renal failure. The histology showed gross glomerular lesions with widespread damage throughout the kidneys. It is pertinent to suggest that the blood transfusions may have contributed to the ultimate renal failure by overloading the circulatory system with extra fluid, though there was never any clinical evidence of pulmonary or generalized oedema. At necropsy Case 1 had a little oedema of the legs and Case 2 showed some periorbital oedema on the day before death.

Prognosis. The prognosis of acute glomerulonephritis in infants under 12 months old is difficult, since very few cases have been fully reported. Cases 1 and 2 fit into Ellis's type 1, though both babies died. The high blood urea levels made the immediate and ultimate prognosis difficult to determine, though high blood urea levels do not always lead to death (Blechmann, 1950). Paterson and Moncrieff (1949) state that 5% of children with glomerulonephritis may die within a few days of the illness, either from the infection or from cardiac or renal failure. Nevertheless, the prognosis of nephritis in children over 2 years old is good. Bernheim (1952) gave a guarded prognosis in acute glomerulonephritis in infancy, especially when it was accompanied by cardiovascular complications, a raised blood urea level, anuria and convulsions. This type of nephritis has at least a 50% mortality. Guthrie (1936) found that juvenile nephritis usually assumed a purer form than in adults, due to the absence of

TABLE

INTAKE AND OUTPUT

Date	Oral (oz.)	Intravenous (ml.)	Urine	Bowel	Vomit
Case 1					
Feb. 28		500 saline	+	1	altered blood +
March 1	11·5	120 blood	++	—	1 ++
2	25		++	—	altered blood ++
3	19·5		++	1 dark stool	—
4	14·5		++	—	—
5	13·5		++	2	1 +
6	18	165 blood	++	1	altered blood 3
7	7		++	1	—
8	13		++	3	—
9	18·5		++	—	2½ oz.
10	19		++	1	1½ oz.
11	18		++	1	1 ++
12	17·25		++	1	2
13	7·25		++	—	1 +
14	6·5	95 blood	+	—	1 +
15	17·5		++	1	—
16	16·5		++	—	1 ++
17	16·5		++	1	1 ++
18	11		++	1	1 ++
19	5	120 blood	+	1	—
20			+		Died 6.30 p.m.
Case 2					
May 20	8		+	—	—
21	18	100 blood	3½ oz. bloody	—	—
22	32		4 oz.	—	1 oz.
23	28·5	115 blood	8½ oz.	1	—
24	25		+ +	1	—
25	23		+++	1	—
26	27		+++	1	1
27	24		+++	—	5 oz.
28	32		+++	—	—
29	28	120 blood	2 oz.	1	2 complete feeds
30	28		+++	—	1 complete feed
31	30		+++	1	—
June 1	20		+++	—	—
2	28		+++	1	1
3	30		spec. grav. 1005	1	—
4	28		+++	1	—
5	24		+++	3	2
6	12	100 blood	+++	4	2
7	18		+++	4	—
8	26		+++	3	1
9	25		+++	7	1
10	15·5		3½ oz.	5	Died 12 noon

arterial disease. Chronic sequelae were rare and the prognosis was good. There were 34 deaths in 477 cases of nephritis (mortality rate 7·12%).

Differential Diagnosis. Both cases are regarded as showing evidence of primary renal damage. The following signs were present: albuminuria, haematuria, oedema, pallor and gastro-intestinal symptoms.

In both infants the pallor was a very prominent feature and it was natural to suspect a primary blood disease, *e.g.*, acute haemolytic anaemia or acute leukaemia. However, the red and white cell counts were normal and there was no jaundice nor any clinical enlargement of the liver or spleen.

Mimicry is one of the outstanding features of nephritis in infancy. Cases 1 and 2 had a little gastro-intestinal upset as shown by vomiting and loose stools. Lévesque, Gouygou and Cousin (1948) report a case of an infant who died from apparent heart failure; the necropsy showed the lesions of acute glomerulonephritis, although during life there were no signs of renal involvement.

Causes of Nephritis in Cases 1 and 2

Heredity. Both infants were born of the same parents, with an interval of 15 months between the births. They were nurtured under good living conditions. Neither infant had any history of previous illness. Both died before they were 7 months old. There was no family history of renal disease. Both parents were healthy and showed no evidence of transmissible disease, *e.g.*, syphilis.

Pathology. The primary lesion was in the glomeruli and not in the tubules. There was no evidence that drugs, especially mercury, ingested poisons, lead paint or aluminium caused this fatal

nephritis. The main clinical features of a rapidly fatal illness were albuminuria, haematuria and pallor. Gross anaemia was present and the blood urea levels were high. Severe renal damage must already have existed when the clinical condition was first apparent.

The main histological findings were a fibrinoid necrosis of some of the afferent glomerular arterioles and gross damage to many glomeruli. Some glomeruli showed pronounced capillary dilatation with hyaline thrombi in their lumina; other glomerular tufts were distorted by adhesions between them and Bowman's capsule. In some instances crescent formation was seen, a lesion which takes four to six weeks to develop. The proximal convoluted tubules showed a generalized dilatation. If this interpretation of the histology is correct, then the renal lesion is a primary glomerulonephritis with secondary changes in the tubules. It is possible that an afferent arteriolar spasm took place in these kidneys with a spread into the glomerular tufts. This was followed by fibrinoid necrosis and thrombosis. The subsequent dilatation of the paralysed blood vessels flooded the glomerular capillary loops with blood, thus causing the haematuria and albuminuria.

The blood pressure readings in Case 2 showed the probable existence of hypertension.

Allergy or tissue hypersensitivity to a toxin has been suggested as a cause of acute nephritis. In Cases 1 and 2 there was never any clinical evidence of a hypersensitive state, *e.g.*, infantile eczema or urticaria. Moreover, there was no known antecedent infection. Both infants had been breast-fed and at 6 weeks were weaned on to National dried milk; they grew and gained weight.

In conclusion, the cause of this glomerulonephritis has not been determined and the following hypothesis has been suggested:

A reservoir of some 'renal toxin' was present at a vital period in the lives of these infants. The toxin might have been produced from the haemolytic streptococcus, group A, type 12. One or both parents might have been temporary carriers of such an organism. At 5 months of age the acquired immunity of the infants had been exhausted and the local conditions, especially in the kidneys, were just right for a 'tissue sensitivity' to be produced by a renal toxin. An acute nephritis developed in these susceptible infants, because they had not yet developed any active acquired immunity to the usual antigens, especially against the streptococcus.

Summary

A fatal acute glomerulonephritis is described in two successive infants of the same family, aged respectively 5¾ months and 6½ months. No cause was found.

Albuminuria, haematuria and anaemia were present and clinical oedema was minimal. High blood urea levels were found at the start of the clinical illness.

The main histological changes were in the glomeruli and in the afferent glomerular arterioles. Some glomeruli showed crescent formation, whilst hyaline thrombi blocked other glomerular capillary tufts. Many tubules were filled by an amorphous eosinophilic material.

Focal sepsis and tissue sensitivity are probably important factors in the cause of nephritis.

The prognosis at this age should be guarded.

The current paediatric literature is reviewed with special reference to nephritis in infants under the age of 1 year. The conclusion is reached that nephritis is rare at this age and little is known of the role of heredity or any familial tendency in this condition.

I extend my sincere thanks to Dr. F. B. Smith of Kendal, Dr. G. Stewart Smith and Dr. F. Brimblecombe of Exeter, and Dr. C. P. Warren of Torquay for their kindness and helpful criticism, and to Mr. Dyson and Mr. Morritt of the pathology department of the Royal Devon and Exeter Hospital.

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HYDRONEPHROSIS IN INFANCY

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Hydronephrosis of the pelvi-ureteric type rarely presents in infancy. Nixon (1953) found only one case in a child under the age of 6 months out of 78 cases seen at The Hospital for Sick Children, Great Ormond Street, between 1929 and 1950. It is, however, a condition which can be treated by conservative surgery and it is important that it should not be overlooked. The following two cases of pelvi-ureteric hydronephrosis are described because they closely resembled other causes of renal enlargement.

Case Reports

Case 1. G.S., a boy, was admitted to The Hospital for Sick Children under Professor Moncrieff on March 18, 1955, at the age of 2 months. His abdomen had been enlarged since birth. For four days before admission he had been vomiting intermittently. He had been having his bowels open three times a day.

On examination he was seen to be a well-fed infant. The abdomen was large and there was divarication of the recti. The liver and spleen were not palpable. There was an easily palpable mass with a smooth rounded lower pole in each loin, the right being larger than the left. The bladder was not palpable. On rectal examination nothing abnormal was found.

The blood urea level was 38 mg. per 100 ml.

A radiograph of the abdomen showed that there was a large soft tissue mass lying posteriorly on each side of the abdomen. There was no calcification in the masses and no abnormality in the spine (Fig. 1).

The provisional diagnosis was of polycystic kidneys.

On the third day after admission the infant's bowels were open five times. The stools were offensive and he lost weight. He was therefore transferred to the gastro-enteritis unit. No pathogens were found in the stools. He was given a week's course of chloramphenicol, but the relaxed stools continued for three weeks and even then did not completely return to normal.

It was noted during this time that the size and tenseness of the loin swellings varied a little from day to day. The possibility of bilateral hydronephrosis was therefore considered and an intravenous pyelogram was performed which showed concentration of dye in each kidney, but detail was grossly distorted.

The blood urea level was now 46 mg. As the diagnosis was still in doubt, a retrograde pyelogram was performed. On April 13 Mr. D. I. Williams performed cystoscopy and a retrograde pyelogram. The bladder, bladder neck and ureteric orifices were all normal. The retrograde pyelogram showed gross bilateral hydronephrosis (Fig. 2).

FIG. 1.—Lateral radiograph of the abdomen of Case 1, showing a huge opacity in the loin.

It was decided that both kidneys should be explored with a view to performing plastic operations, and the right kidney was explored on April 15 by Mr. D. I. Williams.

Through a right loin incision a giant hydronephrosis of the renal pelvis was found. The ureter was of normal size. A Hynes-Anderson (Anderson, 1951) type of

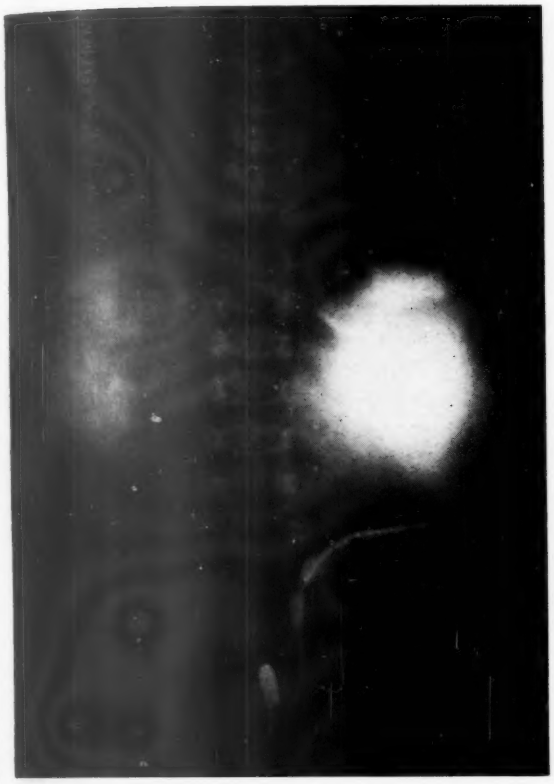

FIG. 2.—Retrograde pyelogram of Case 1, showing bilateral hydronephrosis.

plastic operation was carried out on the pelvi-ureteric junction. A nephrostomy was performed by inserting a Malecot catheter through the renal substance. The wound was closed with drainage.

The nephrostomy tube was removed on the tenth day. Post-operative convalescence from this operation was uneventful.

On May 4 Mr. D. I. Williams found a similar state of affairs as on the opposite side through a left loin incision. A left Hynes-Anderson pyeloplasty was performed and a nephrostomy tube left in to drain the kidney.

The post-operative course was a little more stormy than after the first operation.

The stools returned to normal after the second operation and it was thought possible that the multiple loose stools had been due to a partial obstruction caused by the giant renal swellings.

An intramuscular pyelogram was carried out on June 9, and showed reasonable excretion on both sides.

The patient was finally discharged on June 13, 1955, clinically very much improved.

Case 2. C.E., a girl, was admitted to the Middlesex Hospital under Dr. E. W. Hart on September 22, 1952, at the age of 5 weeks. The abdomen had been distended since birth and an abdominal tumour had been found at the Infant Welfare Clinic. She was taking feeds readily and gaining weight.

On examination she was a small, rather wasted baby. The heart and lungs were apparently normal. The abdomen was enormously distended. There was a small umbilical hernia and there were dilated veins over the abdomen. There was a huge, firm swelling, of smooth outline, filling the right side of the abdomen, which was dull to percussion. On rectal examination, nothing abnormal was found.

Chest radiographs showed that the heart and lungs were normal. There was an abnormality of the posterior part of the right ninth rib, the appearances being in favour of a deposit (Fig. 3).

A radiograph of the abdomen showed a large mass in the right side of the abdomen, arising posteriorly (Fig. 3).

A skeletal survey brought no evidence of any other abnormality.

The provisional diagnosis was of Wilms tumour.

On September 27 Mr. C. J. B. Murray opened the abdomen by a right paramedian incision. A very large retroperitoneal tumour was found in the right loin. When dissected out it proved to be an enormous hydronephrosis of the renal pelvis. The renal tissue consisted of a thin rim stretched out over the surface. The ureter was of normal size. The left kidney was palpated and felt normal. A right nephrectomy was therefore carried out (Fig. 3).

The post-operative course was uneventful. Further radiographs of the ninth rib showed the lesion to be a fracture which had united by the time the baby was discharged on October 21.

Following this operation, she remained well until May 29, 1953, when she was readmitted because she had been off colour for two days. She was found to have an *Esch. coli* pyelitis. The blood urea was 33 mg./

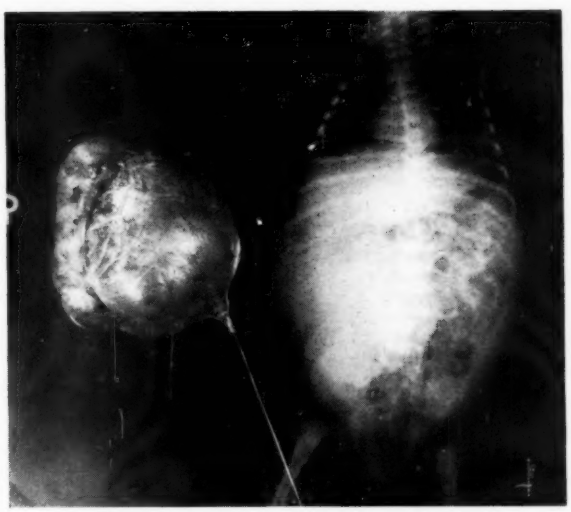

FIG. 3.—Radiograph of the abdomen of Case 2, showing an opacity in the right loin. There is a lesion in the right ninth rib. The hydronephrotic right kidney, removed at operation, is superimposed on the radiograph.

100 ml. The infection responded to sulphafurazole.

An intramuscular pyelogram was performed and showed hydronephrosis of the remaining left kidney.

She was discharged on July 17, 1953.

She was again admitted to the Middlesex Hospital on August 14, 1953, with a temperature of 103° F. and was again found to have an *Esch. coli* pyelitis. The infection responded to sulphafurazole. The blood urea was 37 mg./100 ml.

In view of the two attacks of pyelitis and the finding of left hydronephrosis, it was decided to explore the left kidney.

On September 2 Mr. C. J. B. Murray exposed the left kidney through a loin incision. A hydronephrosis of the renal pelvis was found. The ureter was of normal size. A plastic operation was performed on the pelvi-ureteric junction. A nephrostomy tube was used to drain the renal pelvis.

Recovery from this operation was uneventful. The nephrostomy tube was removed on the seventh day. The child was finally discharged on September 19, 1953, in excellent condition.

She was last seen as an out-patient on December 20, 1954, and was very well.

An intravenous pyelogram performed at this time showed good secretion, though still some hydronephrosis of the left kidney.

The blood urea was 23 mg. per 100 ml.

Discussion

The first case illustrates the importance of differentiating hydronephrosis of the pelvi-ureteric type from polycystic kidneys and from hydronephrosis due to lower urinary tract obstruction. Infantile polycystic disease is very rare in infants who survive more than a few days after birth, and in those who do survive there are almost certain to be signs of severe renal failure. The commonest cause of bilateral cystic enlargement of the kidneys in infancy is lower urinary tract obstruction (Williams, 1955). Most of these infants have congenital valves in the posterior urethra though some have bladder neck obstruction and others congenital strictures of the urethra. The majority present with signs of renal failure and the bladder is usually palpable though sometimes it is quite small. This means that bilateral cystic enlargement of the kidneys in infants, in the absence of renal failure, is most likely to be due to pelvi-ureteric hydronephrosis.

The second case illustrates the difficulty of distinguishing a tense hydronephrosis from a Wilms tumour. Wilms tumour is rare in infancy; during the 25 years from 1925 to 1951, out of 75 cases of Wilms tumour seen at The Hospital for Sick Children, only one was in a child under the age of 6 months.

These cases illustrate the importance of fully investigating all cases of renal enlargement in infancy. If renal failure is absent, an intravenous pyelogram should be performed. If the diagnosis is still uncertain, cystoscopy, urethroscopy and retrograde pyelography should be carried out.

Summary

Two cases of hydronephrosis in infants which were successfully treated by conservative operations are described. The differential diagnosis of renal enlargement in infancy, and the importance of their full investigation is discussed.

My thanks are due to Professor Moncrieff and Mr. D. I. Williams for permission to report Case 1, and to Dr. E. W. Hart and Mr. C. J. B. Murray for Case 2, and especially to Mr. D. I. Williams for his help and encouragement in preparing this paper.

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A HISTOCHEMICAL STUDY OF PULMONARY HYALINE MEMBRANE

BY

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At necropsy on premature infants, microscopic examination of the lungs often reveals the presence of eosinophilic material which forms a hyaline membrane in the alveoli and bronchioles. There seems little doubt of the close association between the intense respiratory distress observed clinically and the presence of this membrane at necropsy. However, there is, as yet, no general agreement on the pathogenesis of the condition, and the controversy is more than academic for it seems that a rational therapeutic approach must await a satisfactory explanation of its origin.

The relevant literature on hyaline membrane up to 1952 has been reviewed by Tran-Dinh-De and Anderson (1953). Broadly, there are two main schools of thought. First, the advocates of aspiration of amniotic fluid ('exogenous aetiology'), though at present in the majority, appear to be losing ground. Secondly, there are those who consider that the membrane is formed in alveoli and bronchioles *in situ* and that it is the result of vascular injury. Increasing evidence in support of this concept is appearing in the literature. There are a few workers who call on factors, both exogenous (aspiration) and endogenous (exudative), in an attempt to produce an acceptable thesis (Stevenson and Laufe, 1955).

Having studied the methods adopted hitherto to find out the basic structure of hyaline membrane it was considered that it would be possible and rewarding to pursue this fundamental aspect further. A strong bias towards the endogenous theory on clinical grounds was a purposeful stimulus along a difficult road which, however, already had some signposts for which earlier workers must be thanked. This paper is, therefore, an account of some avenues explored in an attempt to discover the nature of hyaline membrane.

Morphological studies by Gilmer and Hand (1954) led them to postulate an endogenous origin for the eosinophilic material primarily from the blood stream, and they considered also that an additional possibility was an alteration of the basement membrane to form the hyaline substance or, alternatively, the formation of it between capillary and pulmonary basement membrane. Lynch and Mellor (1955) concluded from their histological studies that 'hyaline membranes' represent a highly concentrated secretion from the epithelial cells of the terminal bronchioles and alveolar ducts.

It seemed more profitable to study the hyaline membrane of infants in comparison with eosinophilic material occasionally found in pulmonary oedema or in other parts of the body such as in thrombosed vessels, or in the albuminous precipitate surrounding some glomeruli of the kidney. By the use of a whole battery of various staining techniques it was possible to demonstrate that the different precipitates behaved, from that aspect, in a similar manner (Table 1). The results of the methods employed suggested strongly that the hyaline membrane

TABLE 1
STAINING REACTIONS

Stain	Hyaline Membrane	Pulmonary Oedema	Thrombus	Glomerulus Precipitate
Haematoxylin and eosin	Red	Red	Red	Red
Periodic-acid-Schiff	Positive	Positive	Positive	Positive
Southgate's mucicarmine	Brownish	Brownish	Brownish	Brownish
Prussian blue	Negative	Negative	Negative	Negative
Van Gieson	Yellow	Yellow	Yellow	Yellow
Thionin	Negative	Negative	Negative	Negative
Methylene blue	Negative	Negative	Negative	Negative
Phloxine tartrazine	Red	Red	Red	Red
Carbol fuchsin	Yellowish	Yellowish	Yellowish	Yellowish
Congo red	Negative	Negative	Negative	Negative
Gram-Weigart	Negative	Negative	Negative	Negative
Gentian violet	Faint	Faint	Faint	Faint
Sudan IV	Negative	Negative	Negative	Negative
Mallory's trichrome	Orange	Orange	Orange	Orange
Masson's trichrome	Reddish	Reddish	Reddish	Reddish

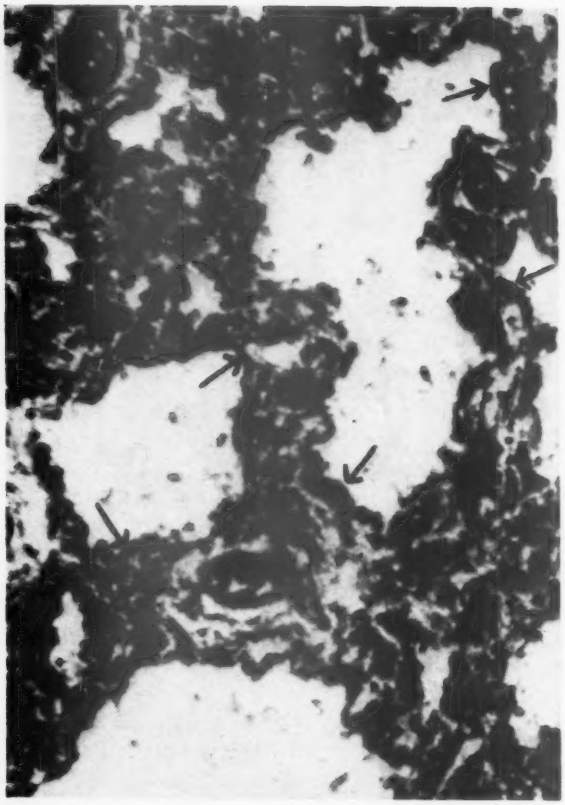


FIG. 1.—Lung of a recently born baby containing hyaline membrane stained with the Pickworth technique. The hyaline membrane gives a positive reaction.

FIG. 3.—Acellular material found in a lung vessel thrombus stained with the Pickworth technique. The intravascular material gives a positive reaction.

FIG. 2.—Pulmonary oedema stained with Pickworth technique. The exudate gives a positive reaction.

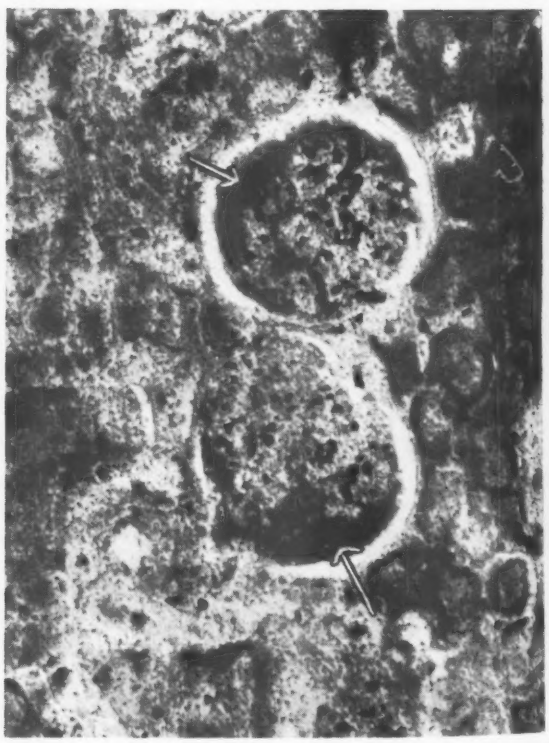
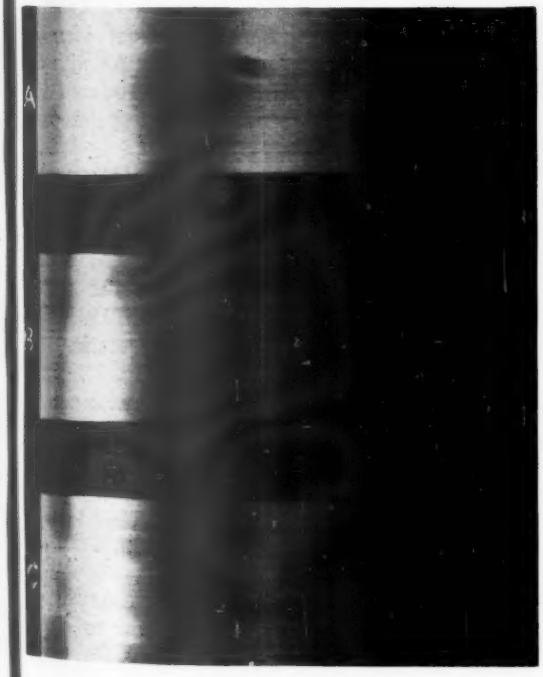


FIG. 4.—Exudate round a renal glomerulus stained with the Pickworth technique. The exudate gives a positive reaction.

FIG. 5.—Fluorescence of hyaline membrane using Wood's light, green filter and auramine.

FIG. 6.—Continuous spectrogram of A, blank; B, red blood cells; C, hyaline membrane. The similarity can be seen between B and C.

FIG. 7.—Mercury vapour light spectrograms of A, blank; B, red blood cells; C, hyaline membrane. The similarity between B and C can again be seen.



belonged to the group of cytochromes derived from blood proteins and pigments and, therefore, the Pickworth technique (as described in Pearse, 1953) commended itself for further study. All the materials examined gave a positive peroxidase reaction* (Figs. 1, 2, 3, 4). In view of these results attention was directed to other techniques employed in the investigation of blood derivatives. Under ultra-violet light using a Wood's filter (Wagner, 1950), the hyaline membrane showed a faint but definite primary fluorescence. On staining the relevant sections of lung with auramine the hyaline membrane showed, as expected, this phenomenon much more clearly (Fig. 5).

To test further the relationship between hyaline membrane and the haemoglobin group, a capillary containing blood and a blank control giving the absorption of lenses and glass slides were submitted to microspectrography using a technique described in a previous communication (Ardern and Duran-Jorda, 1953). Using a Tungsten light the three spectrograms were taken on the same photographic plate. The hyaline membrane showed absorption in the same region of the violet band as the blood in the capillary vessel (Fig. 6).

* The results of work using this technique were demonstrated to the Section of Pathology of the Manchester Medical Society.

←FIG. 6

FIG. 7→

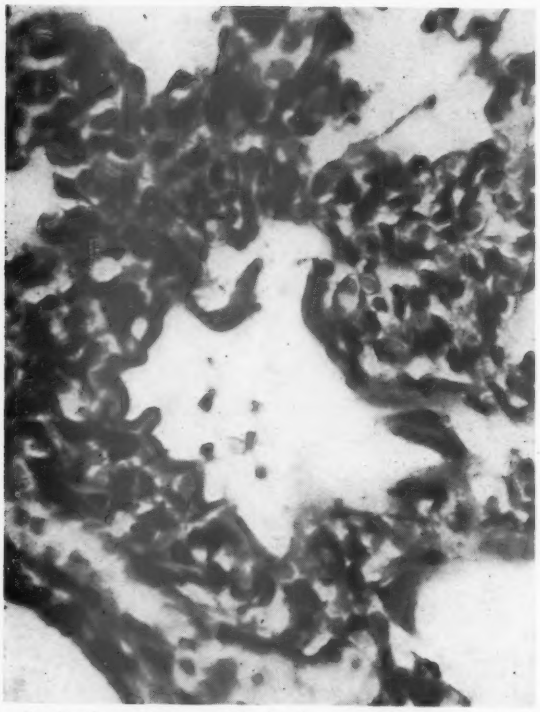


FIG. 8.—Section of lung with hyaline membrane stained with haematoxylin and eosin.

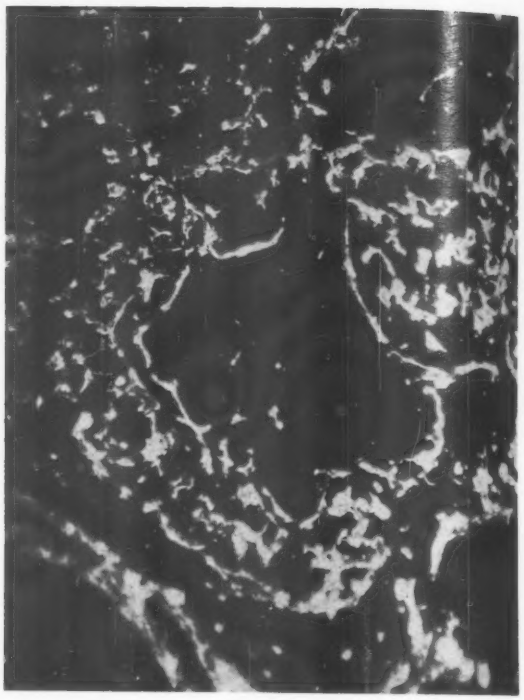


FIG. 9.—The same field after micro-incineration demonstrating the ashes left by the hyaline membrane.

In order to confirm this finding the absorption of the hyaline membrane was studied under a mercury vapour lamp, as its light produces four prominent lines of absorption in a fixed part of the spectrum. Comparing again the spectrogram of hyaline membrane and blood in a capillary from the same section in the fourth band (the area in which blood pigments show maximal absorption), an almost identical spectrographic pattern was obtained. As with the Tungsten light a blank control was introduced and the three spectra photographed on the same plate (Fig. 7).

FIG. 10.—The same micro-incinerated field under polariscopic light showing the silica contained in the hyaline membrane.

As an additional step to explore the basic structure of the hyaline-like material and, at the same time, to eliminate the possibility of its consisting of fat or gluco-proteins (mucus), sections of the lung with hyaline membrane were submitted to the drastic process of microincineration (Scott, 1933). A selected microscopic field of the same section was photographed and then incinerated (Fig. 8). Subsequently, the same field was examined with a dark condenser and a second photograph taken. It could be easily observed that the hyaline membrane left a considerable amount of ashes (Fig. 9). Some of these were red, indicating the presence of iron salts, and examination under polarized light showed also a silica content (Fig. 10).

At this stage it was decided to study the material remaining after dialysing amniotic fluid to determine if there was any hyaline substance. Polythene

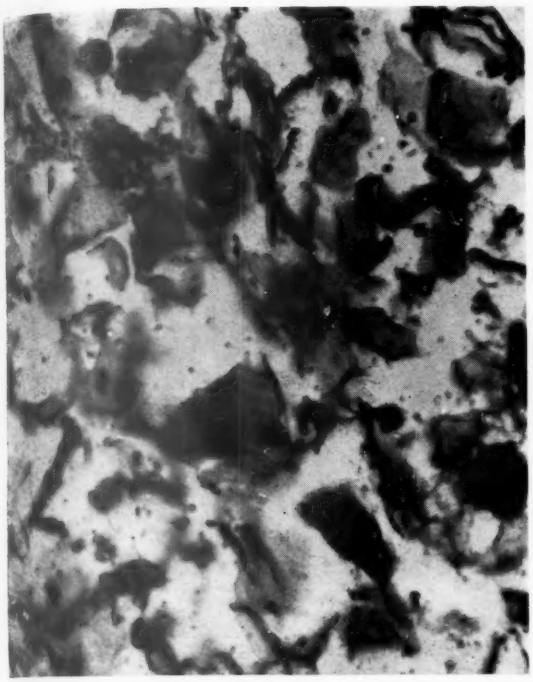


FIG. 11.—Section of amniotic fluid remnants after dialysis showing epithelial cells and debris, but no eosinophilic material.

tubing was used and a 10% solution of dextran as dialysing fluid. The residue, a firm white substance, was collected, fixed in formol saline and embedded in paraffin. After sectioning and staining the remnants were seen to be composed entirely of epithelial cells. No eosinophilic material could be found (Fig. 11).

Discussion

The work described was undertaken because it was felt that the continued belief that hyaline membrane was the result of inhalation of amniotic fluid was not contributing to an understanding of its pathogenesis and so far had not led to a satisfactory therapeutic approach.

The basic fact is that while the membrane is found mainly in newborn premature babies it has been found in the lungs outside the neonatal age group in a number of conditions. For example, exposure of the lungs to high oxygen concentrations in aviation has resulted in the formation of the membrane (Ingalls, 1954). In some instances such hyperoxia has produced a combination of haemorrhagic pneumonia and membrane formation. This finding is of particular interest because of the clinical impression that there is a close association between the so-called haemorrhagic pneumonia of the newborn and hyaline membrane disease (Fig. 12). Often it would seem to be merely a matter of degree.

Lendrum (1955) postulates that the pulmonary hyaline membrane is a manifestation of left heart failure in the newborn premature infant. He feels that the familiar terminology as at present used is objectionable because 'it centres attention upon a single and possibly minor member of a highly constant group of manifestations'.

It was not the purpose of this paper to claim that hyaline membrane disease is a clinical entity. Sufficient evidence is available to suggest that histology reveals an end-result rather than a cause. It is claimed, however, that the evidence produced here weighs heavily in favour of an endogenous origin for pulmonary hyaline membrane, and that it is a blood derivative. This being so it would seem to follow logically that the present therapeutic effort of trying 'to dissolve the membrane' by medicated mists, etc., is not the proper line of approach, and appears about as futile as trying to cure faucial diphtheria by scraping the membrane off the throat.

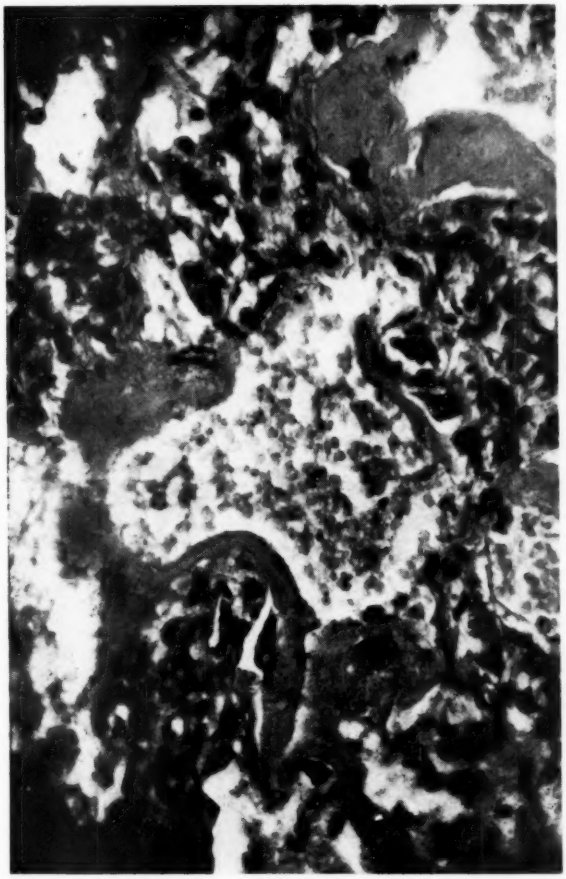


FIG. 12.—Section of haemorrhagic newborn lung with a very thick hyaline membrane.

Summary

A planned series of laboratory investigations to determine the nature of hyaline membrane is described. It is concluded from these investigations that the membrane is derived from the lung capillaries. Its nature suggests that it follows intense congestion of the alveolar capillaries which result in an exudative process through the capillary walls. It seems to be an end-result rather than a cause, and capable of explanation without postulating aspiration of amniotic fluid. The complete absence of hyaline material from amniotic fluid is noted.

Our thanks are due to Drs. Crawford and Langley for supplying some of the pathological material and to Dr. Bevis for help with the work on amniotic fluid. Mr. T. Walsh's painstaking technical assistance was much appreciated. The Hospital Management Committee made a generous grant from the hospital's research fund.

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RADIOLOGICAL FINDINGS IN THE LUNGS OF PREMATURE INFANTS

BY

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What is the place of the radiologist in the diagnosis and treatment of the ailments of the premature infant? First, he must be able to recognize the variations in the normal premature baby's chest and abdomen. Secondly, he must attempt to give the clinician some idea of the identity of the pathological changes in the lungs. Thirdly, and probably his most important function, is to try and help the paediatrician to distinguish between the respiratory distress which is primarily cerebral in origin and that due directly to pathological changes in the lungs.

These infants cannot readily be moved down to the main *x*-ray department in the average hospital in this country, nor is it advisable to do so. We, therefore, use a standard mobile *x*-ray apparatus with a minimum time exposure factor of 0·05 seconds, which is kept permanently in the premature babies' ward, and as soon as the infant arrives in the ward it is laid on a casette in the incubator and a radiograph of the chest and abdomen taken. The initial radiograph may be the only one, for it has been considered that no further films are justified in an infant who exhibits no significant respiratory distress and is thriving. If, however, there is any obvious alteration in the clinical progress, radiographs are taken at appropriate intervals.

Using the methods described, a surprisingly high percentage of the films taken have been of very good quality, and few have been useless for diagnostic purposes. It is fully realized that the technique is far from ideal, but it has been considered that any radiograph was better than none at all.

The advisability of disturbing the premature infant to carry out this procedure may well be questioned, but it was felt that the chance of arousing intercurrent infection was slight, that the amount of disturbance to the infant was not significant, and that the degree of radiation was negligible.

Certain variables and artefacts make the interpretation of these radiographs far from simple. The phase of the respiratory cycle makes a quite extraordinary difference in the apparent degree of aeration of the lung fields, and the phase of contraction of the heart also alters the pattern to a considerable degree. These appear to have a greater variant effect in the first few hours of life than at a slightly later stage. Another artefact which may show is the presence of vertical lines over the lung fields which may simulate a pneumothorax under certain conditions. These are due to the skin folds caused by the lack of subcutaneous fat in the premature infant.

The displacement o the heart to the left, which has been seen in a fairly high percentage of these cases, is in my opinion due to the plasticity of the thoracic cage and the consequent sternal suction inwards.

During the last 18 months 190 infants have been examined by this radiographic technique in the premature babies' ward at Crumpsall Hospital, Manchester. The great majority were delivered in the Hospital, but a few came in from the District within an hour or two of birth.

Forty-nine of these did not survive, and the cause of their deaths is shown in Table 1. Of the remaining cases, 25 showed pathological changes in the radiographs of the lungs and clinical respiratory distress (Table 2).

TABLE 1
CAUSE OF DEATH IN 49 PREMATURE INFANTS

Primary lung unexpansion from all causes, including prematurity		12
Miscellaneous causes		11
(i) Associated congenital anomalies	4	
(ii) Unexplained	4	
(iii) Suprarenal haemorrhages	3	
Cerebral deaths with lung expansion		9
Hyaline membrane		7
Neonatal pneumonia		5
Sclerema		3
Haemorrhagic disease of the newborn		2

It has been stated (Martin and Freidell, 1952) that the lungs of the newborn do not become fully expanded for up to six days and that primary atelectasis may be shown histologically for that

period in full-term infants, whilst it may take up to six weeks for the premature infant fully to expand the lungs.

TABLE 2

PATHOLOGICAL CHANGES IN 25 INFANTS

Diffuse primary alveolar atelectasis	9
Incipient hyaline membrane	4
Pneumonia	3
Cerebral injury with good lung expansion	3
Congenital cardiac lesions	2
Mongol	1
Miscellaneous	3

I have taken serial radiographs of a number of full-term children at caesarean section from eight seconds to 12 minutes after the cutting of the cord, and have found that there is complete expansion of the lungs radiologically—in the majority by six minutes. I consider that this rapid adequate aeration is of far greater practical significance than the microscopical unexpansion of small areas of lung.

A different state of affairs obtains in the radiographs of lungs of premature infants, in whom I have observed that practically every chest examined radiologically within an hour of birth showed some fairly well marked areas of unexpansion. These were mainly in the lower lobes, and were undoubtedly more marked on the left than on the right side. In uncomplicated cases these areas showed fairly complete expansion within six to eight hours.

Pulmonary Conditions in Present Series

Pulmonary conditions observed in the present series may be broadly divided into the following categories:

(*a*) Prematurity or immaturity, leading to complete or almost complete primary atelectasis;

(*b*) Intracranial lesions resulting in primary unexpansion of the lungs;

(*c*) Intracranial lesions allowing expansion of the lungs initially;

(*d*) Primary lung lesions

- (i) Hyaline membrane
- (ii) Neonatal pneumonias
- (iii) Diffuse primary alveolar atelectasis
- (iv) Haemorrhagic disease of the newborn

(*e*) Congenital cardiac lesions. (These have not been specifically studied in this series.)

(a) Prematurity or Immaturity. Plain uncomplicated immaturity (described by the coined word 'anectatos', Farber and Wilson, 1933), may lead to unexpansion of the lungs for a variety of interrelated reasons. Of these the major considerations appear to be the immaturity of the lungs, the poverty of the respiratory effort and the excessive plasticity of the thoracic cage.

This type of unexpansion follows the pattern of primary atelectasis or unexpansion, which is seen in other forms of this catastrophe, and can only be distinguished from them by the maturity of the infant and knowledge of the time after birth that the radiograph had been taken. The larger bronchi are clearly outlined against the practically opaque lung parenchyma. The outlines of the heart and diaphragms are hazy and the cardiac shadow is often displaced to the left. A histological study of these lungs generally shows terminal anoxic haemorrhages into many of the alveoli with large areas of alveoli which have never been aerated, showing cubical rather than pavement epithelium lining them.

Bowel gas shows sluggish motility and the infant practically never survives.

(b) Intracranial Lesions Resulting in Primary Unexpansion of the Lungs. There are types of intracranial injury which occur during parturition which are so widespread or devastating that the infants' respiratory centre is severely damaged at that time. They do not make adequate respiratory efforts, and, like those who die of their prematurity, the lungs never become adequately expanded. The radiological appearances are not distinguishable from those of grossly premature infants except by their greater bone maturity and size. The bowel gas progresses poorly, though this picture may be falsified by the use of intragastric oxygen.

(c) Intracranial Lesions Allowing Initial Expansion of Lungs. In general, tentorial tears and intraventricular haemorrhages are progressive in their effects upon the respiratory centre, and there is reasonable expansion of the lungs initially in most of these cases.

With increasing damage to the brain from haemorrhage and with failing respiratory effort, areas of atelectasis become apparent in the radiographs. These do not take on the miliary pattern of hyaline membrane and there is not usually enough atelectasis in the lung fields to suggest a pure respiratory death, except in radiographs taken in the completely terminal stages. There the familiar pattern of the 'blacked-out' lung is seen with its opaque lung fields, vanished cardiac silhouette and obliterated diaphragmatic outlines.

The guiding radiological feature in the diagnosis of progressive intracranial damage is, in my opinion, the discrepancy between the relatively slight degree of atelectasis in the lung fields and the severity of the respiratory distress.

(d) Primary Lung Lesions. These fall into four classes.

(i) PULMONARY HYALINE MEMBRANE. Hoccheim described this condition first in 1903. The radiological appearances have not received much attention until recently, when they were fully described by Steiner (1954) in this country and by a number of other authors, mainly in the United States.

The cases in this series conform well to the pattern described by Steiner. There is some unexpansion at birth, but fair respiratory effort. This is followed by a miliary mottling, which tends to be fairly widespread but may be somewhat localized. These changes may be present in the early radiographs, but always manifest themselves within 12 hours of birth. As the disease progresses the mottling takes on a coarser and more generalized appearance, followed by atelectasis of a blotchy type. Eventually, after a period of increasing collapse and consolidation, the blacked-out lung of the terminal stage makes its appearance.

The clinical condition keeps step with the radiological findings, and the infant rarely survives more than 30 hours.

There is another radiological pattern which may be suspected as incipient hyaline membrane. In this, the lung fields show the miliary mottling previously described, and in which they may go on to show a coarser mottling, but do not go beyond the phase of minor lobular atelectasis. As the clinical condition improves the mottling slowly fades, but cases have been seen in which it has persisted for six to seven days.

Histological proof that this is indeed the hyaline membrane syndrome is of course missing, but, as Donald and Steiner (1953) point out, the clinical features tie up very closely with the earlier manifestations of the known fatal type of hyaline membrane.

(ii) NEONATAL PNEUMONIAS. I do not think that it is possible to distinguish between the pneumonias of the immediate neonatal period, whether they be due to metastatic infection from the maternal circulation, inhaled infected liquor during parturition, or post-natal infective processes. In the present series there were nine cases of what was considered to be pneumonia. Six of these were proven at necropsy, and three of them survived, but clinically and radiologically were typical of the condition.

The common pattern was that of a bronchopneumonia radiologically, but two showed a confluent lobar pattern which involved the right upper lobe.

(iii) DIFFUSE PRIMARY ALVEOLAR ATELECTASIS. There is another group of infants, some of whom survive, the radiographs of whose lung fields show a ground glass appearance which is evenly distributed throughout. The pattern is not that of hyaline membrane, and even in those who do not live does not develop into the coarse mottling and type of atelectasis associated with that condition. This radiological appearance is associated with some degree of respiratory distress which is usually surmounted. When the infant has not survived, the post-mortem findings in the lungs have been those of considerable areas of primary alveolar atelectasis histologically, and an absence of hyaline membrane.

I have observed this condition radiologically as early as seven minutes after birth, when it was already distinguishable from the normal at that age. It is possible, in my opinion, to distinguish it from hyaline membrane, and thus give a more hopeful prognosis.

This condition appears to be a less severe form of primary alveolar atelectasis, and I would, therefore, describe it as diffuse primary alveolar atelectasis.

(iv) HAEMORRHAGIC DISEASE OF THE NEWBORN. Only two cases of this condition were radiographed in the present series, both of which failed to survive. In the first, a rather confident radiological diagnosis of pulmonary hyaline membrane was made. In the second, and without clinical information, it was suggested that the appearances in the radiograph were not entirely typical of hyaline membrane but might be those of haemorrhagic disease of the newborn.

The radiological picture differed only very slightly in the two conditions. The small areas of atelectasis causing the miliary mottling in the lung fields seemed rather larger on the whole than those of hyaline membrane, and appeared rather more discrete. It was felt, however, that the distinction was a very fine one and that it was not possible to separate the radiological appearances of the two conditions with any confidence.

(e) Congenital Cardiac Lesions. No attempt was made specifically to investigate the congenital cardiac lesions or other congenital anomalies observed in this series.

Clinical Cases

It must be realized that the radiological patterns in the neonatal lung are generally so delicate that it is not possible adequately to describe them in a paper; particularly is this true of the diffuse primary alveolar atelectasis. Therefore only examples of those conditions showing distinctive changes will be singled out for demonstration.

Immaturity. The following case illustrates the pattern found in immaturity.

J. G., a boy, of 25 weeks' maturity (weight 1 lb. 2½ oz.) was the first child of his mother from whom no obstetric history of note was obtained, and whose labour was uncomplicated.

The infant's condition was poor, but respiration was regular, and he gave a few squeaky cries. His condition steadily deteriorated and death took place three and a quarter hours after birth.

RADIOLOGICAL FINDINGS. At one and a half hours (Fig. 1) there was primary atelectasis of most of both lung fields with the main and secondary bronchi outlined against the semi-opaque lung tissue. The diaphragmatic and cardiac outlines were poorly defined. At three hours a film was taken as the baby was *in extremis*. The blacked-out lung fields were shown.

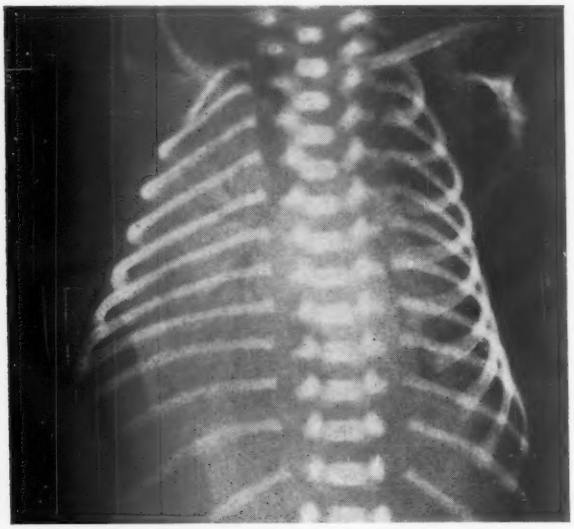

FIG. 1.—Primary atelectasis of most of both lung fields, with the main and secondary bronchi outlined against the semi-opaque lung tissue.

POST-MORTEM FINDINGS. There were no significant findings except in the lungs, which, though pink, sank in water.

HISTOLOGICAL FINDINGS. In the right upper lobe very little aeration had occurred, and the features were those of primary non-expansion; no membrane.

The right lower and left upper lobes had not expanded primarily; no membrane. In the left lower lobe there were intra-alveolar haemorrhages and the lobes had not expanded primarily; no membrane.

Hyaline Membrane. The case of D.W., a girl of 36 weeks' maturity (4 lb. 4 oz.), illustrates the findings with hyaline membrane.

The mother had had six pregnancies with one still-birth. There was an obstetric history of A.P.H. at 30 weeks and labour lasted one hour 35 minutes. The mother was febrile in labour, and the placenta was unhealthy.

FIG. 2.—Coarse mottling and greatly increased atelectasis, and bowel gas only in the ileum.

The infant was pale and shocked with limited air entry into the lungs. The sternum was sucked in and cyanosis steadily deepened until death at seven hours and 50 minutes after birth.

RADIOLOGICAL FINDINGS. At 35 minutes there was a fair degree of unexpansion with a fair mottling throughout the lung fields, changes suggestive of hyaline membrane.

Gas in the bowel progressed onward relatively poorly. At 3 hours mottling had increased with further atelectasis. At 6 hours 40 minutes (Fig. 2) there was coarser mottling with greatly increased atelectasis, and bowel gas only in the ileum. At 7 hours 50 minutes the blacked-out lung of death was seen.

POST-MORTEM FINDINGS. Pathology was limited to the lungs in which there was considerable secondary atelectasis and well marked hyaline membrane. There were residual areas of primary atelectasis.

Neonatal Pneumonia. The following case illustrates the findings in neonatal pneumonia.

D.B., a male twin, of 37 weeks' maturity (4 lb. 4 oz.) was born of a mother who had already had one pregnancy. There was no obstetric history of note and labour was uncomplicated.

The infant's condition was good and the lung expanded satisfactorily for the first two days after birth, after which he collapsed with convulsions and occasional gasping inspirations, dying some 12 hours later.

RADIOLOGICAL FINDINGS. At 1 hour 20 minutes there was satisfactory expansion of both lung fields, with the slight unexpansion one might expect in a premature infant at that stage. At 2 days there was still good expansion of the lung fields. Intragastric oxygen was being given. At 2 days 12 hours (Fig. 3) a film was taken almost at the point of death. There was consolidation of the right upper lobe and some atelectatic changes of the right lower lobe. There were also pneumonic changes in the left upper lobe.

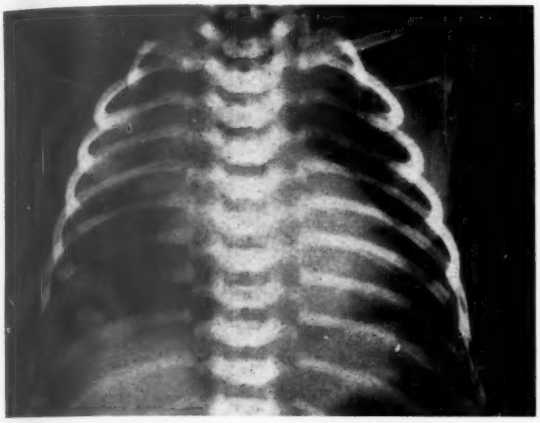

FIG. 3.—Film taken at the point of death.

POST-MORTEM FINDINGS. Pathology was limited to the lungs, which showed pneumonic consolidation of the right upper lobe and the adjacent part of the lower lobe.

HISTOLOGICAL FINDINGS. The alveoli were filled with polymorphs and the bronchioles contained polymorphs as well. There were some amniotic squames. The appearances were those of a confluent bronchopneumonia.

Conclusions

The radiographs of 190 premature infants have been examined in the present series, and it is considered that this ancillary investigation may help the clinician considerably in his conduct of the cases.

From this limited preliminary survey I think that it is possible to distinguish radiologically between the acute respiratory distress due to an intracranial lesion and that of a pulmonary condition.

The radiological appearances of pulmonary hyaline membrane are fairly clearly defined, but may be closely simulated by those of haemorrhagic disease of the newborn involving the lung and certain phases of neonatal pneumonia.

The condition I have termed 'diffuse primary alveolar atelectasis' appears to me to be generally distinguishable from hyaline membrane, and to have a more favourable ultimate prognosis but further investigation is necessary on this point.

I would like to thank Dr. Patterson, who is in charge of the Premature Babies' Ward at Crumpsall Hospital, for his stimulation to carry out this investigation and his help in doing so. I would also like to thank Dr. Davson for his interest and cooperation in correlating the histological and radiological pictures.

Finally, I would especially thank Sisters Thornley and Maclaren, who have been responsible for taking the majority of the radiographs and whose interest and help in this project have been invaluable.

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SINGLE POLYP OF THE LARGE INTESTINE IN CHILDHOOD

BY

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A single polyp of the large intestine is a well recognized entity. It is found in both children and adults and is to be differentiated from familial adenomatosis of the large intestine, which has been fully reviewed by Lockhart-Mummery and Dukes (1939).

The presenting symptom in most cases is rectal bleeding which may be of a chronic nature or may be severe. Other symptoms are prolapse of the polyp through the anal canal, intussusception or obstruction. The polyp may undergo malignant change.

Case Report

Janet H., aged 8, one of six children, was admitted to Morriston Hospital on July 27, 1955, with a history of severe bleeding per rectum and central colicky abdominal pain for 24 hours. She had been constipated for three days.

On admission, physical examination revealed no abnormalities. Digital examination confirmed the presence of red blood in the rectum. The father produced a specimen of a pint of bright red blood clot and mucus passed before admission. There was no history of rectal bleeding in other members of the family.

Blood was given intravenously. The patient suffered two further attacks of severe rectal bleeding and laparotomy was advised. The descending and pelvic colon contained blood. A small, nodular thickening in the pelvic colon was examined and excised after opening the bowel. No polypi were palpated in the large or small intestine. The patient made an uneventful recovery. Sigmoidoscopy and barium enema examinations later revealed no evidence of polypi.

On the night of admission the father produced a large polypoid mass, about the size of a walnut, which he retrieved from the pan used by the child at home (Fig. 1). Pathological section of the nodule removed at operation revealed normal colon mucosa. The section report on the polyp read: 'Adenomatous polyp made up of tall columnar mucus-secreting epithelium with well marked chronic inflammatory reaction. No sign of malignant change.' This polyp had amputated itself and the severe bleeding occurred from the mucosal end of the amputated stalk.

Discussion

How often does self-amputation occur? Numerous cases of rectal bleeding in infancy and childhood happen for no apparent reason. It is reasonable to suggest that in these cases a single adenomatous polyp has amputated itself and that the extruded polyp has been lost.

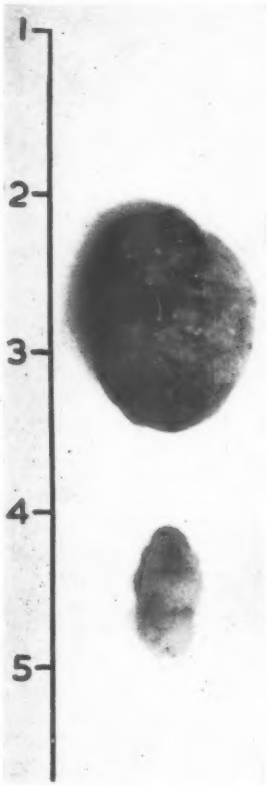

FIG. 1.—Photograph of the polyp extruded by the patient (scale in inches).
The smaller nodule was excised at operation.

The incidence of single or multiple polypi in children is unknown, but the figure generally quoted

is about 3%. In a series of 70 cases of rectal bleeding in children under 6 years of age investigated by Harris (1953), 48 had polypi in the rectum, 16 in the sigmoid and six above the sigmoid colon; 52 were single polypi only. In eight cases there was self-amputation of the polyp, an incidence of 11·4%, and four of these were brought to the surgery by parents. He comments that the number of cases that get well by self-amputation seems remarkable. In another series of 349 cases, reported by Kerr (1948), 100 had polypi, of which 68 had a single polyp only. He states that 'frequently a single episode of severe melaena may be evidence of self-amputation of a polyp (18 cases) and the tumour may be produced by an intelligent parent'. The incidence of self-amputation in this series was 18%. Kerr states that self-amputation is frequent in children, but rare in adults.

Summary

A case of self-amputation of a single polyp of the large intestine is reported. The incidence of the polypi is about 3%. Malignant change may occur. It seems very likely that many cases of rectal bleeding in infancy and childhood follow self-amputation and extrusion of a polyp of the large intestine. The chance of this occurring is not established; the two figures quoted place it at 11·4% and 18%.

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BLOOD PRESSURE IN THE NEWBORN ESTIMATED BY THE FLUSH METHOD

BY

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The increasingly widespread practice of careful routine examination of the newborn infant, particularly where it reveals a cardiac murmur, has increased the need for a simple method of measuring neonatal blood pressure.

As assessed indirectly, widely varying blood pressures have been recorded in the newborn. Sphygmomanometric estimation by the standard methods of auscultation and palpation is nearly always difficult and time-consuming and often impossible. Recently a simple rapid method, using the flush principle applied by Gaertner to blood pressure estimation more than 50 years ago, has been employed in newborn infants (Cappe and Pallin, 1952; Goldring and Wohltmann, 1952). This method has not yet been entirely standardized however. Its accuracy has been proclaimed (Reinhold and Pym, 1955), and has been doubted (Schaffer, 1955), and the normal range of newborn blood pressure as so measured has not yet been fully established.

This paper reports a series of 513 blood pressure estimations carried out by the flush method on 143 full-term normal newborn infants. Nearly all of these were carried out during the first 11 days of life. The readings were taken in pairs on the arm and leg, and as far as possible two pairs were taken on each infant during the 11-day period.

Method

The technique was modified from the methods described by Goldring and Wohltmann and Cappe and Pallin.

All readings were taken in good diffuse daylight with the baby in his cot in the right lateral position. The infants were clothed and the nursery temperature was 65-70° F.

Readings were not made routinely after feeding and no sedation was used. A standard mercury sphygmomanometer was used and it was always applied to the left arm and left leg, each being used first in alternate cases. An average of two readings or, where any difficulty was experienced in determining the end-point, an average of three readings, was taken.

A 3-in. rubber Martin's bandage was firmly wrapped round the limb from the periphery to mid-calf or mid-forearm, and a 4-in. × 2-in. sphygmomanometer cuff was then applied to the thigh or arm respectively. The pressure was then raised to about 130 mm. of mercury and the rubber bandage rapidly removed, a pallid extremity being obtained with a well demarcated edge. The pressure was lowered 6 mm. and left at this level for five seconds while the limb was inspected. This procedure was repeated until flushing developed. The first warning that the flushing point was approaching was obtained from the fine oscillation which developed in the mercury column. (This oscillation began 5 to 10 mm. above the flushing point and was maximal on reaching this point.) The pressure was then lowered carefully, a few mm. at a time, until flushing occurred. This consisted in a sudden loss of definition of the line of demarcation and a fine pink flush spreading distally at a varying pace depending upon the amount of activity of the infant. If the infant was asleep or very quiet the development of this fine flush was more tardy in appearing and more easily missed. Further lowering of the pressure produced a vivid red flush confined to the previously blanched area. This reaction was presumably due to plethora (secondary to occlusion of the venous return) developing in the previously exsanguinated distal portion of the limb and was considered to be beyond the true end-point.

If the limb was kept blanched for too long passive diffusion of the blood from deeper tissues occurred, blurring the zone of demarcation and interfering with the accuracy of readings. Hence it is important to arrive at the vicinity of the end-point as expeditiously as possible.

Occasionally difficulty was experienced in producing a satisfactory pallid zone. The true explanation of this is not known, but it may have been due to seepage of blood out of tissues splinted by the long bones from the pressure of the bandage.

Unlike Goldring and Wohltmann and Reinhold and Pym, we applied the cuff round the upper arm and thigh rather than the lower arm and lower leg lest the splinting

effect of the double bones in the latter two situations might permit a leak of blood into the portion of the limb distal to the cuff and result in false readings.

Results

Age. Table 1 and Figs. 1, 2 and 3 show the mean pressures in arm and leg according to age with ranges calculated in terms of twice and thrice the

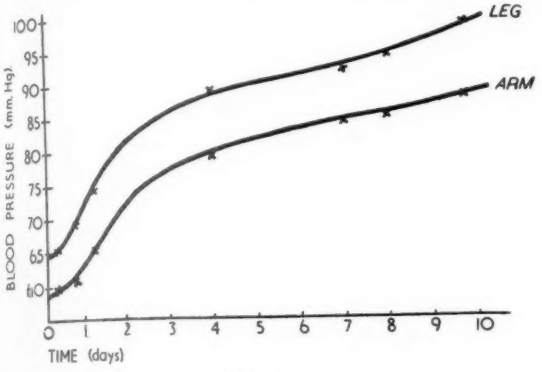

FIG. 1.

standard deviation from those means (95·5% of readings would be expected to be within the range, mean $\pm 2 \times$ S.D. and 99·7% within the range, mean $\pm 3 \times$ S.D.). The mean birth weights of each of the age groups were sufficiently close for weight not to be a factor in the production of any alteration of blood pressure. The rise in blood pressure over the 11-day period is statistically significant.

On direct measurement of the blood pressure in the umbilical artery at birth, Woodbury, Robinson and Hamilton (1938) found a range of pressure of

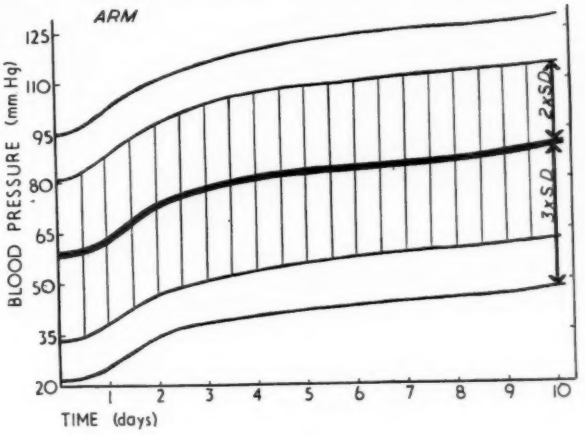

FIG. 2.

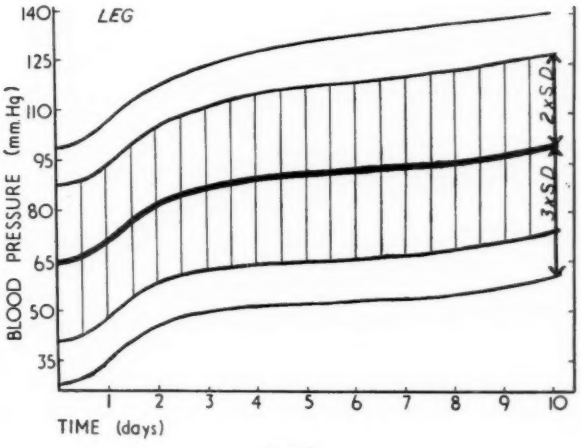

FIG. 3.

TABLE 1
BLOOD PRESSURE AND AGE

Age	Number of Readings	Mean Pressure	Standard Deviation	Range (Mean$\pm$2$\times$S.D.)	Standard Error of Mean	Coefficient of Variation	Mean Birth Weight (lb.)
0–12 hr. (Av. = 7·2 hr.)	A. 37 L. 38	59·5 65·4	12·0 11·7	35·5– 83·5 42·0– 88·8	4·0 3·8	20·4 17·9	7·5
13–24 hr. (Av. = 18·8 hr.)	A. 43 L. 45	60·5 68·8	13·6 12·7	33·2– 87·7 43·4– 94·2	4·2 3·8	22·4 18·3	7·3
24–48 hr. (Av. = 29·9 hr.)	A. 23 L. 23	65·1 73·7	12·4 10·5	40·3– 89·9 52·7– 94·7	5·2 4·4	19·0 13·6	7·8
2–6 days (Av. = 4 days)	A. 22 L. 22	79·0 88·7	13·9 13·0	51·2–106·8 62·7–114·0	3·8 5·6	17·3 14·9	7·5
7 days	A. 29 L. 29	84·4 91·7	12·2 12·2	60·0–108·8 67·3–116·1	4·6 4·6	15·2 13·3	7·1
8 days	A. 52 L. 52	85·0 94·3	14·7 15·7	55·6–114·4 62·9–125·7	4·0 4·4	16·3 15·8	7·4
9–11 days (Av. = 9·7 days)	A. 43 L. 43	88·3 99·0	13·4 12·0	61·5–115·1 75·0–123·0	4·0 3·6	15·2 12·4	7·1

A. = Arm L. = Leg

TABLE 2
BLOOD PRESSURE AND WEIGHT

Weight Group (lb.)	Mean Pressure	Standard Deviation	Standard Error of Mean	Number in Group	Average Age of Group
5–7 (Av. = 6·27)	A. 70·3 L. 79·5	17·3 17·4	1·7 1·7	103 103	4·8 days
7–8 (Av. = 7·44)	A. 76·7 L. 84·2	17·0 17·6	2·0 2·0	73 75	4·7 days
8–11 (Av. = 8·65)	A. 80·2 L. 88·3	18·2 18·9	2·1 2·2	73 74	4·8 days

A. = Arm L. = Leg

64 to 96 mm. of Hg systolic and 30 to 63 mm. of Hg diastolic, and also showed that the pressure in the umbilical artery is approximately the same as that in the brachial artery. Ssladkoff (1903) using a modified Gaertner tonometer found the mean blood pressure in the first 24 hours to be 61 mm. Hg; Rucker and Connell (1924) found the mean pressure at birth to be 55 mm. Hg systolic and 40 mm. Hg diastolic.

The rise in blood pressure in the first 12 days of life, rapid during the first three days and slower thereafter, is in keeping with the findings of Ssladkoff (1903), Balard (1912), Reis and Chaloupka (1923), and Woodbury *et al.* (1938). Ssladkoff also showed that the blood pressure ceases to rise after one month and that it rises very little from then until the age of 7 or 8 years.

Weight. Table 2 shows the mean blood pressure of infants in the three groups according to birth weight, 5 to 7 lb., 7 to 8 lb., 8 to 11 lb. The mean ages of the infants in each of these groups were practically identical, thus age was not a factor in the difference between them. These results are shown graphically in Fig. 4. The rise in blood pressure with increasing birth weight is statistically significant.

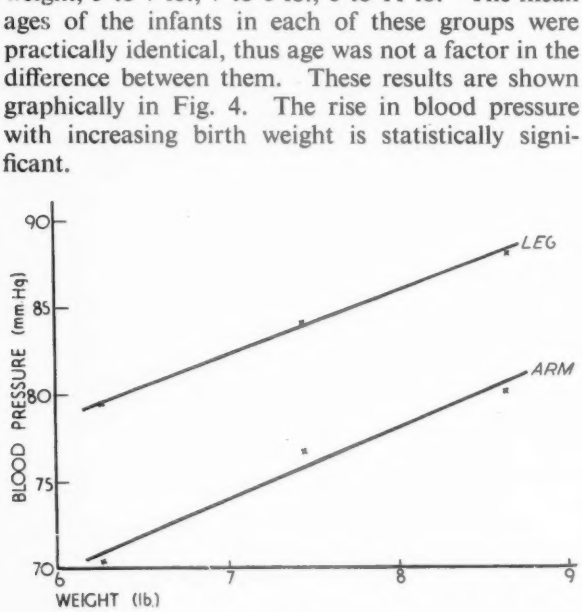

FIG. 4.

The coefficient of correlation between birth weight and blood pressure (i.e., the mean of the four blood pressure readings taken over the 11-day period) was + 0·297. The standard error was 0·0945. There is thus a significant positive correlation between blood pressure and birth weight.

It is possible that a factor in the higher blood pressure with increased birth weight is the greater length and girth of the upper arm relative to the size of the cuff. It is unlikely, however, that this wholly accounts for the difference, as Sullivan and Kobayashi (1955) found no correlation between blood pressure measured by the flush method and weight in a group of 160 infants whose ages ranged from 8 to 11 months. The varying length and girth of the upper arm in this group therefore did not influence the blood pressure.

Comparison of Blood Pressure in Leg and Arm. By applying the cuff to the upper arm and thigh the differential between arm and leg pressures, present in older children and in adults and probably also in the newborn (Robinow, Hamilton, Woodbury and Volpitto, 1939), is usually revealed. There is no such differential when the cuff is applied to the forearm and the lower limb (Goldring and Wohltmann, 1952; Reinhold and Pym, 1955).

In 231 out of 256 pairs of blood pressure recordings (90·2%) the leg pressure was equal to, or higher than, the arm pressure; in the remaining 25 pairs (9·8%) the leg pressure was lower than the arm pressure. One hundred and sixteen infants had pairs of blood pressures taken on two occasions at approximately weekly intervals. Out of the 232 pairs of pressures taken, 23 showed a reversed leg/arm pressure differential, but only twice was this reversed pressure present in the same infant on both occasions. In only six out of the 25 reversed blood pressures could crying (during the arm pressure but not during the leg pressure) have been a factor in the reversal. In the 25 reversed pressures the mean of the ratios expressing the leg

TABLE 3
EFFECT OF CRYING ON BLOOD PRESSURE

Age (days)	Crying				Not Crying				Percentage Increase on Crying	
	Arm		Leg		Arm		Leg		Arm	Leg
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.		
0–3½	67·4	14·4	78·4	11·7	63·9	10·7	73·4	8·5	5·5	6·8
6–11	92·6	13·5	99·9	13·5	84·4	12·5	94·1	14·3	9·7	6·2
0·11	84·9	17·8	94·4	15·8	78·1	15·1	88·7	15·8	8·7	6·4

Mean increase in pressure on crying = 7·5%

pressure as a percentage of the arm pressure was 89·9% and the standard deviation was 8·3% (S.D. × 3 = 24·9%). At three times the standard deviation therefore the lowest expected ratio would be 65% and this would occur very infrequently.

Thus, using the routine described here on normal newborn infants during the first 11 days of life there is only a 1 in 9 chance of the blood pressure in the legs being less than that in the arms, there is a 1 in 200 chance of the leg pressure being less than 75% of the arm pressure and only a 1 in 3,000 chance of the leg pressure being less than 65% of the arm pressure. Where two blood pressure estimations are carried out on the same infant with an interval of a few days between, in less than 5% of normal infants will the pressure in the legs be less than that in the arms on both occasions.

On the average the arm/leg blood pressure ratio for the various age groups specified in Table 1 remained constant at approximately 0·9. The widest individual variations from the average, however, were seen in the first two days of life. After the fifth day no leg pressure was less than 85% of the arm pressure.

These standards are likely to have their greatest use in the diagnosis of coarctation of the aorta.

Effect of Crying. Fifty-two arm blood pressures and 54 leg pressures were taken on 67 crying infants. Each crying infant has been paired off with another of practically equal age and weight who was not crying at the time of blood pressure estimation, and the blood pressures compared. No infant was used more than once in the latter group. The results are shown in Table 3. Thus over the first 11 days of life crying increased blood pressure by less than 10% in the arm and less than 7% in the leg. None of these increases is statistically significant. These figures for crying and non-crying infants are given with some reserve as it was often difficult to decide whether an infant should be recorded as crying or not. Crying might cease just as the blood pressure estimation was about to begin or occur very transitorily during the estimation. Also the infant might be restless without actually crying.

By other methods crying has produced a significant effect. Woodbury *et al.* (1938) found that it raised the blood pressure by a mean percentage of 34 and Hoen (1952), measuring blood pressure by a method depending on transillumination of the external auricular artery, that it caused a rise ranging from 30 to 100%. These comparisons were made on the same patient crying and not crying.

Sex. Table 4 shows the blood pressure in the arm and leg in males and females in the first three and a half days, from the sixth to eleventh day, and over the 11-day period. The mean weights and ages of the males and females of the two groups were practically the same. It will be seen that the sex of the infant has no influence on the blood pressure at this age.

Assessment of Accuracy of Results by the Flush Method. Some assessment of the accuracy of the flush method can be made by comparing the results obtained by this method with those obtained on direct catheterization on the assumption that the variability of the latter represents the true variability

TABLE 4
EFFECT OF SEX ON BLOOD PRESSURE

Sex	Arm 0–3½ days	Arm 6–11 days	Leg 0–3½ days	Leg 6–11 days	Average of Arm and Leg 0–3½ days	Average of Arm and Leg 6–11 days	Average of Arm and Leg 0–11 days
Male ..	63·2	87·2	70·5	95·2	67·0	91·2	79·4
Female ..	63·3	84·6	71·3	95·0	67·3	89·8	80·0

of blood pressure. Woodbury *et al.* (1938) found the mean umbilical artery pressure in 24 infants at birth to be 80 mm. Hg with a coefficient of variation of 10. We took 24 pressure readings in the arms within eight hours of birth and the coefficient of variation of our results was 18. Using the same mean as Woodbury *et al.*, therefore, the range that would be expected by the flush method would be 51 to 109 mm. of Hg as compared with the true range of 64 to 96 mm. of Hg.

The actual range of our under-eight-hour pressure readings extended over 43 mm. Hg (42-85); that of Schaffer (1955), using the method of impendence plethysmography on 24 infants at birth, extended over 50 mm. Hg (52-102).

Thus it would appear that the flush method, although not so accurate as direct measurement, and not so accurate as the auscultatory method, which in the older child or adult gives results closely comparable with direct pressure recordings, is yet sufficiently accurate to be a useful clinical guide. The range of results by this method might be further narrowed by ensuring that all pressures were taken with the infant quiet.

In the newborn infant, pressure readings obtained in the upper arm with a 1-in. cuff show more variation than those obtained with a 2-in. cuff (Reinhold and Pym, 1955; Schaffer, 1955), but are most truly comparable with direct readings of the systolic pressure (Woodbury *et al.*, 1938). We used a 2-in. cuff and the readings which we have obtained are thus probably below the systolic pressure. They are likely, however, to be fairly close to the mean systolic-diastolic pressure as our mean arm pressure by the flush method in the first eight hours (60 mm. Hg) agrees closely with the mean systolic-diastolic pressure (63 mm. Hg) observed by Woodbury *et al.* on direct measurement.

Summary

Five hundred and thirteen blood pressure estimations have been carried out on 143 newborn infants (aged 0-11 days) using the flush technique.

The technique is described.

An assessment is made of the accuracy of the method and it is concluded that, although it is less accurate than the auscultatory method in the older child or adult, it is a useful clinical procedure.

The pressures given by the method described represent approximately the mean systolic-diastolic blood pressure.

During the first 11 days of life blood pressure increases significantly with age and shows a positive correlation with birth weight.

The normal range of blood pressure in the first 11 days of life is given.

In 90% of readings the blood pressure in the leg is higher than that in the arm.

The probabilities of occurrence of various degrees of reversed arm/leg pressures which may be encountered in the normal newborn infant are given.

Crying was found to increase the blood pressure by an average of 7·5%.

No sex difference was found.

We wish to thank Professor R. W. B. Ellis for his support.

We also wish to acknowledge the invaluable help given by Sister Stephen in carrying out the blood pressure estimations.

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COEXISTENT APLASTIC ANAEMIA AND COARCTATION OF THE AORTA

BY

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(RECEIVED FOR PUBLICATION DECEMBER 19, 1955)

The association of hypoplastic anaemia with congenital abnormalities in children has been recognized since 1927 when Fanconi described three such cases. Several further instances of this Fanconi syndrome have been reported; in each, the congenital anomalies have been multiple and have affected particularly the bones, eyes, genitalia and skin. Only one case has been described (Estren, Suess and Dameshek, 1947) in which cardiovascular abnormality is specifically mentioned: this was an 11-year-old girl with a patent ductus arteriosus and/or atrial septal defect (an exact diagnosis was not made, but the lesion was clearly congenital); she was also undersized, had a pigmented skin, nerve deafness, and bony anomalies of the thumbs, forearm and carpus.

In the following case the hypoplastic anaemia was associated with only one obvious congenital defect, coarctation of the aorta.

Case Report

A 14-year-old boy attended his doctor with a history of recent severe epistaxes, weakness and exertional dyspnoea. He was pale and had a faint scattered purpuric rash; the heart seemed slightly enlarged and a short apical systolic murmur was heard. Finding some nasal ulceration, his doctor gave a course of sulphamezathine: this proved unhelpful, and the boy was referred to hospital for further medical advice. A provisional diagnosis of thrombocytopenic purpura was made in the out-patient department and the patient was soon admitted for full investigation.

He had always been subject to nose bleeds but these had been worse in the last few weeks. For a year he had bruised easily, and latterly bruises had been appearing spontaneously. He was getting paler. His legs ached, and he had palpitations when he hurried. Previously he had been quite fit. His father and two sisters (aged 6 and 9 years) were well; his mother suffered from occasional attacks of asthma.

He was a short, thick-set boy of normal mentality; he was pale, and had scattered bruises and petechiae over the chest, arms, and trunk; the liver and spleen were not palpable; there was no lymphadenopathy; the blood pressure was 160/100 mm. Hg, and there was a systolic murmur over the precordium; the urine was normal; he showed no skeletal, neurological or ophthalmological abnormalities; there was no sign of puberty, and the genitalia were small but normal; the skin was not pigmented.

The blood count showed: Hb 5·3 g. %, R.B.C. 1·31 millions per c.mm., W.B.C. 1,500 (N. 30%, L. 60%, E. 4%, M. 6%); no platelets were seen in the blood film; there was a 2% reticulocytosis. The bleeding time was over 30 minutes (Duke's method) and the clotting time 5 minutes (Lee and White's method); Hess's tourniquet test was positive; the blood group was A Rh positive. No red bone marrow was obtained with a sternal puncture, but an iliac crest puncture was more successful. The marrow was very sparsely cellular: the granulocytes showed primary aplasia and maturation arrest at the myelocyte-metamyelocyte level; the red cell precursors were reduced in number but were maturing normally; no megakaryocytes, and no cells more immature than premyelocytes or proerythroblasts, were seen.

A diagnosis of aplastic anaemia having been made, the boy was given a transfusion of packed red cells. He improved considerably, and was allowed home. Oral iron and proteolysed liver were ordered.

Less than a week later he was readmitted with more petechiae and increasing pallor. The blood count had fallen, and a further packed cell transfusion was given. During his stay a detailed examination was made of the cardiovascular system: this revealed unequivocal evidence of coarctation of the aorta. No abdominal aortic pulsation and none of the leg pulses were palpable; the systolic blood pressure was 145 mm. Hg in each arm, 95 mm. Hg in the right leg and 90 mm. Hg in the left; pulsation could be felt and heard in the suprascapular and superficial epigastric arteries. The heart was slightly enlarged, and a grade 3 murmur could be heard, closely following the first heart sound, over the precordium, down the spine, and over the palpable vessels. There was no evidence of aortic regurgitation. A chest radiograph showed slight left ventricular enlargement, a dilated ascending aorta, no aortic knuckle, and 'notching' of the fourth, fifth, sixth and seventh ribs posteriorly. The immediate management of the case

was unaffected by these findings, and the boy was obliged to attend regularly for blood transfusions, 3 pints of blood being required every two or three weeks. At no time was there any evidence of spontaneous improvement in the pancytopenia. Nevertheless, the boy was able to lead a fairly normal life.

Although the two pathological conditions were presumed to be unrelated, there was a possibility that subacute bacterial endocarditis could be the link between them. A persisting evening pyrexia was an additional reason for investigation. Successive blood cultures were negative, however, and the boy's good general condition, appetite and vitality were well maintained.

The clinical course was punctuated after four months by a very severe epistaxis for which he required repeated nose-packing and a total of 11 pints of blood. Six months later, two series of severe epistaxes required the transfusion of 16 additional pints of blood. The end came a few weeks afterwards, when the boy suddenly began vomiting and became unconscious, with signs of cerebral haemorrhage. He died two hours later without regaining consciousness. He had survived 12 months from the date of diagnosis, and during that time had received a total of 86 pints of blood. (It is a remarkable tribute to the laboratory staff that, despite the large number of transfusions, no reactions occurred and no irregular antibodies were ever detected by the albumin tube or Coombs tests.)

The post-mortem examination showed a large left cerebral haemorrhage, multiple small scattered haemorrhages in nearly all the organs and a typical severe adult-type aortic coarctation without other congenital cardiovascular defects. The marrow cavity of the right femur contained only soft yellow fatty tissue. At death, the boy was 15 years 4 months old; he was 5 ft. 2 in. in height and showed no signs of puberty. Otherwise he was of normal physical and mental development.

Comment

This association of pancytopenia with aortic coarctation could be considered merely coincidental, but as Reinhold, Neumark, Lightwood and Carter (1952) point out, 'Aplastic anaemia (in children) . . . is sufficiently rare to make an association with other congenital malformations by chance a remote possibility.' The moderate underdevelopment of the skeleton and genitalia in the present case may have been significant in the circumstances. Admittedly, the child showed no microcephaly, localized bone anomalies, squint, mental defect, spasticity, renal abnormality, pigmentation, gynaecomastia or other peculiarities, and his two sisters are quite normal children. Thus he clearly did not fall within the generally accepted bounds of the Fanconi syndrome (Estren and Dameshek, 1947; Reinhold *et al.*, 1952). But it does seem possible that he represented a sporadic *forme fruste* of this condition, there being an incomplete manifestation of the inherent chromosomal defect postulated by Fanconi. An alternative possibility—remote, but important from the practical standpoint—was that the pancytopenia could have been a manifestation of occult subacute bacterial endocarditis (Parsons, Cooper and Scheifley, 1953). But the clinical, bacteriological and (later) pathological findings excluded this.

It seems most unlikely that 'partial ischaemia' of the centres of haemopoiesis (which nearly all lie distal to an aortic coarctation) could have been a factor in the pathogenesis of the hypoplastic anaemia. But the two primary conditions doubtless acted synergically in at least two ways: the tendency to epistaxis, and the final cerebral haemorrhage (a common cause of death in both).

My thanks are due to Dr. Frank Robertson for permission to publish, and to Dr. J. M. Robertson for the pathological reports.

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SUBCUTANEOUS EMPHYSEMA COMPLICATING ASTHMA

BY

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Subcutaneous emphysema complicating asthma is a somewhat rare condition and when first met with rather an alarming one. Subcutaneous emphysema as a secondary manifestation of trauma of the chest wall, fracture of the orbit with escape of air from the nasal sinuses to the neck and thorax, or on occasion complicating tracheotomy or thoracentesis, is probably more common, and the mechanism whereby the air reaches the subcutaneous tissues is certainly more easily understood.

Elliott (1938) reports subcutaneous emphysema in a woman of 46, developing at the onset of an asthmatic attack and followed two days later by a partial pneumothorax. In this case the subcutaneous emphysema was generalized and was not relieved until an incision was made over the chest wall; whereupon she deflated with a loud hissing sound. Field (1943) reports a case of a girl aged 4 years 2 months in whom subcutaneous emphysema complicated an acute attack of asthma. In this case the emphysema subsided, but 12 days later she developed a spontaneous pneumothorax and massive collapse.

Case Report

A girl aged 6 years 2 months was admitted to hospital as an emergency on October 22 with an attack of asthma. She had been having minor attacks of asthma, lasting approximately half-an-hour and subsiding without treatment, since the age of 16 months. During the last three months, the attacks had been more frequent and had lasted longer. The present attack had started on waking on the morning of admission; it was more severe than any she had had previously, and when she was seen was of some eight hours' duration.

Apart from frequent tonsillitis, she had had no previous illness, or eczema during infancy. Her paternal grandfather had asthma.

On admission she looked ill, and the lips were cyanosed. There was audible expiratory wheezing (temperature 100·4° F., respirations 60 per minute, pulse 160). On examination of the chest the movements were equal but poor, the trachea central. The breath sounds were harsh, and there were sibilant rhonchi predominantly expiratory over both lung fields.

She was given adrenaline, 4 minims subcutaneously, crystalline penicillin, 250,000 units six-hourly, 'gantrisin', 1 g. six-hourly, phenobarbitone, ¼ grain, and oxygen by mask immediately.

There was some improvement following the subcutaneous adrenaline, and it was thought that she would probably settle down and have a good night. However, she was restless and vomited three times during the night. The following morning her condition had obviously deteriorated, and on questioning she admitted to having had a severe pain in the left chest. The respiratory rate was now 70 per minute, pulse 170 per minute, and temperature 101° F. The cyanosis was more marked and had an unusual maroon tinge. She was obviously in great distress.

On examination there was surgical emphysema extending around the neck, over the left chest and axilla, and down to the left flank. The heart appeared to be normal, the trachea was central, but the movement of the left chest was reduced and the breath sounds on the left almost absent.

A radiograph of the chest (Fig. 1) showed that both lungs were well expanded, and that there was marked surgical emphysema in the neck, the left axilla and in the mediastinum. She was given 'nepenthe', 8 minims, and put in an oxygen tent.

Her general condition improved almost immediately. Half-an-hour later her respiration rate had fallen to 50 per minute and four hours later was 20 per minute. The surgical emphysema did not increase in degree, but the following day had spread to the right chest. It then gradually subsided and in six days had entirely gone.

On discharge seventeen days after admission she was very well and the chest was clinically and radiologically clear (Fig. 2).

Discussion

It seems well established that for air to reach the subcutaneous tissues from the lungs in this type of case it must first reach the mediastinum. Once it has reached there it may proceed via the neck to any part of the body, as there is no anatomical barrier to stop its advance.

The mechanism within the lung has been well investigated by Macklin (1939) by introducing a

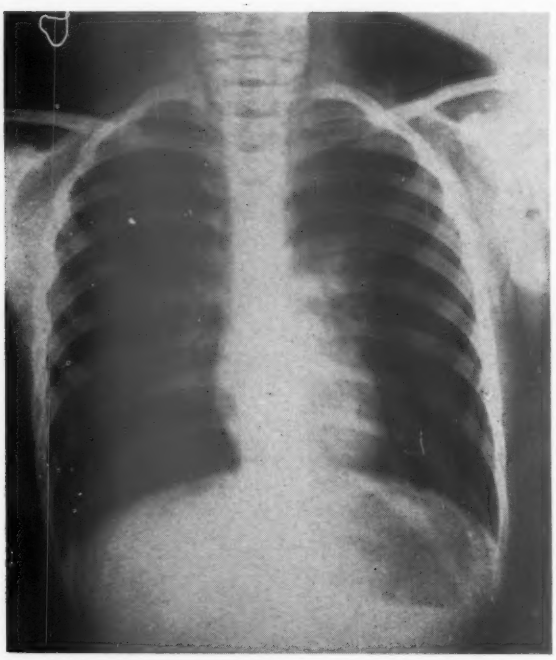

FIG. 1.—Chest radiograph taken on the morning after admission, showing marked surgical emphysema.

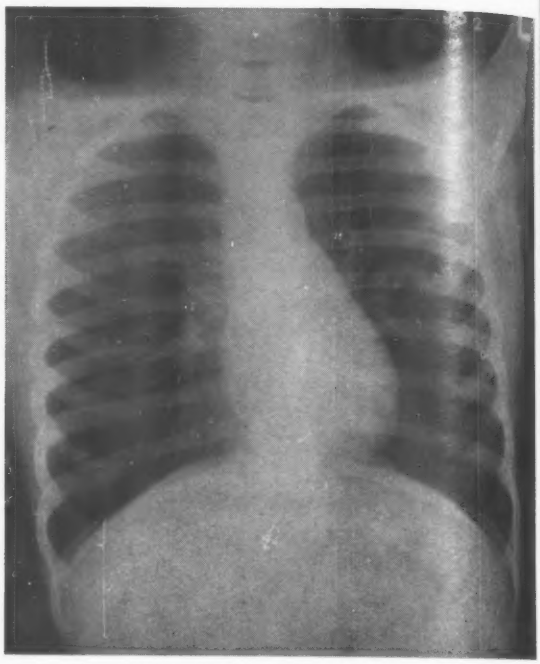

FIG. 2.—Chest radiograph 17 days after admission, showing complete absorption of the surgical emphysema.

catheter into a region of an animal's lung and over-distending the alveoli. He found that the air leak was due to multiple and very fine ruptures in the alveolar bases, and that the escaping air travelled along artificial tunnels formed in the vascular sheaths. Further, within the lung it may take one or both of two routes: (1) To the mediastinum, from which there may be serious consequences, owing to an interference with the pulmonary blood flow due to the increased pressure in the perivascular sheaths at the root. It seems reasonable to suppose that this was the cause of the sudden increase of dyspnoea and tachypnoea of our patient, and that the aching pain complained of during the night was ischaemic in nature and secondary to a partial occlusion of the pulmonary blood flow. (2) The escaping air may equally track peripherally, and here form a bulla beneath the visceral pleura, and it seems reasonable too to suppose that rupture of a bulla so formed may be the cause of a spontaneous pneumothorax which occasionally complicates an acute attack of asthma without there being subcutaneous emphysema, or of the spontaneous pneumothorax which may occur at a variable time after the appearance of subcutaneous emphysema as in Field's case.

The prognosis of this condition seems to be good, and in a review of the literature by Rosenberg (1938), 18 cases of subcutaneous emphysema complicating asthma made a complete recovery, the emphysema disappearing in from two to 21 days. The ages of these patients ranged from 3 to 38 years.

The treatment of our case consisted of antibiotics. This is important because the artificial channels made by the air escaping from the ruptured alveoli make excellent pathways for bacteria to reach the lung parenchyma and the mediastinum. Secondly, sedation; 8 minims of 'nepenthe' intramuscularly was sufficient, and great improvement followed it. This immediately brings up the question of whether 'nepenthe' should be given to patients having an asthmatic attack; certainly in this type of case it seems to be indicated. Oxygen was given, partly as the cyanosis and respiratory distress warranted it, but also with the idea that if the subcutaneous air consisted mostly of oxygen it would absorb more quickly than if the nitrogen content were high. There was no need to remove the air artificially, as the emphysema was not massive and absorbed quickly. However, in cases where there is extreme subcutaneous emphysema, an incision is more likely to have the desired effect than attempting to aspirate. Finally, if the side from which the air is escaping can be localized, the induction of an artificial pneumothorax on that side, with the object of collapsing the lung and so preventing further escape of air from the alveoli would seem to be a logical form of treatment.

Summary

A case is reported of a girl aged 6 years 2 months who showed subcutaneous emphysema complicating an attack of asthma. The probable mechanism, likely complications and methods of treatment are discussed.

I wish to thank Dr. Charles Newman for permission to report this case, and for the help and encouragement he gave me in preparing the paper.

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CLINICAL ASPECTS OF CONGENITAL TUBERCULOSIS

BY

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Congenital transmission of tuberculosis is rare. In the past the diagnosis has usually been made in the post-mortem room and the condition has interested the pathologist more than the clinician. In the majority of published cases the nature of the illness has been apparent soon after birth. In others, however, the symptoms have not appeared for several weeks or months and it is not easy to accept all of these as true examples of congenital transmission of the infection, even though they fulfil all the criteria detailed by Beitzke (1935), for it is well known that a very brief exposure to an adult with phthisis may be sufficient to infect an infant.

Since streptomycin became available about a dozen cases have been diagnosed early, treated and apparently cured. In this paper another successful case is recorded and the symptoms, diagnosis and management are discussed.

Case Report

A female infant was born in Walton Hospital on November 2, 1953, three weeks before the expected date and weighing 5 lb. 12 oz. (2,632 g.). Her mother had developed pleurisy with effusion when five months pregnant. She had responded well to treatment without antibiotics and was afebrile for several weeks before going into labour. A week after parturition her temperature again rose, but a radiograph of the chest showed thickening of the basal pleura only. Two weeks later another radiograph showed miliary tuberculosis. She was treated with streptomycin and isoniazid and she made a good recovery.

The infant was segregated from her mother immediately after birth and did not come into contact with any other case of tuberculosis. She was vaccinated with B.C.G. (0·1 ml.) in the left arm on the second day of life. Her progress was uneventful until the eighteenth day when she lost 2 oz. (57 g.) and seemed lethargic. The next day a respiratory infection was suspected and chloramphenicol prescribed. Three days later her condition had deteriorated and there were signs of consolidation in both lungs. Material aspirated from the stomach the same morning (the nineteenth day of life) contained many acid-fast bacilli, and a radiograph taken the day previously showed generalized bronchopneumonia. Treatment with streptomycin and isoniazid was started forthwith. She was nursed in an 'oxygenaire' incubator with a high humidity and occasional periods of oxygen administration. During the next three or four weeks she remained very ill. She fed badly, vomited at times and had severe dyspnoea with inspiratory recession of the lower chest. The spleen became palpable and almost reached the level of the iliac crest. Eventually there was considerable improvement in the chest signs and radiological appearances, but she did not gain weight. Chemotherapy was stopped after three months. Her weight was then 6 lb. (2,736 g.). In the next two months she gained 1½ lb. (694 g.), but at the age of 6 months there was clinical and radiological deterioration. A second course of treatment with streptomycin and isoniazid lasted three months. During this period she gained 4 lb. (1,816 g.) in weight and the clinical signs in the chest improved considerably. On her first birthday she weighed 17 lb. 6 oz. (7,925 g.). She was then able to sit without support, could almost stand and took a lively interest in her toys and surroundings. A radiograph of the chest showed basal congestion in the lung fields and some increase in the mediastinal shadow. The B.S.R. was 9 mm. in one hour (Westergren) and haemoglobin 12 g. %. At the age of 18 months she still appeared very well and weighed 20 lb. 3 oz. (9,205 g.).

During the first course of treatment she developed a purulent discharge from the right ear and this continued intermittently for about one month. Tubercle bacilli were not isolated from this discharge and there has been no recurrence. During the second course of treatment a fluctuant swelling developed in the right groin. This was incised and caseous material was expressed from which tubercle bacilli were cultured. The lesion soon healed and has not given further trouble. There were never any meningeal signs and the C.S.F. was not examined. The eyes were examined frequently but no choroidal tubercles were seen.

There was very little local reaction to the B.C.G. vaccination. Though potent testing material was used the Mantoux reaction remained negative until the seventh month of life.

Tubercle bacilli were cultured from stomach washings obtained on the nineteenth day of life and again in April, 1954, and in February, 1955. None were found in samples taken in July, 1954. Bacilli cultured from the inguinal lesion in August, 1954, were fully sensitive to streptomycin, isoniazid and P.A.S.

Discussion

The Clinical Picture. Much of the literature about congenital tuberculosis deals with the pathological aspects of the disease and only the more recent reports give many clinical details.

Usually the symptoms start during the first month of life and are those common to any infection in the newborn period. The infant refuses some feeds, vomits a little and loses weight. The temperature may be raised. The spleen is often enlarged and sometimes the liver. A cough and physical signs of bronchitis or pulmonary consolidation have been recorded on some occasions, but there have also been instances of extensive lung involvement with few clinical indications of its presence. In more than half of the reported cases the infant has died within three or four weeks of the first sign of illness, and the diagnosis has been made at necropsy.

The shortest history was recorded by Horley (1952). Apparently well during the first week of life, the infant had a cyanotic attack on the eighth day and died 24 hours later. Post-mortem examination revealed miliary tuberculosis.

Hughesdon (1946) records the longest survival without treatment. This infant suffered from frequent attacks of bronchitis and otitis media and latterly symptoms suggesting pink disease. She was not taken to hospital until the age of 27 months when her weight was 21 lb. (9,575 g.). Tuberculous meningitis was diagnosed a few days after admission and she died two weeks later. At necropsy a primary focus was found in the liver and this was held to confirm congenital transmission of the infection. Amick, Alden and Sweet (1950) reported two cases where the presenting sign was enlargement of the cervical glands. In one infant this was noticed at the age of 56 days. The chest radiograph was then clear but two weeks later showed miliary tuberculosis, and the gastric washings contained tubercle bacilli. The other infant had fever and enlarged neck glands at 49 days, followed by right otorrhoea and right facial paralysis. Material obtained from the mastoid bone and biopsy of a lymph node showed tuberculous lesions. Surprisingly the chest radiographs of this baby remained clear throughout the illness. Both were considered to be undoubted cases of intra-uterine infection and both recovered after streptomycin therapy.

Obstructive jaundice was a prominent feature in four cases (Hughesdon, 1946; Debré, Furiet-Laforet and Royer, 1948; Ballabriga Aguado, 1950). One infant developed deep jaundice and pale stools at the age of 1 month then recovered and lived for nearly a year before dying from miliary disease. A focus assumed to be the primary infection was found in the liver. Another infant became acutely ill at 14 days with vomiting, abdominal distension and jaundice. Tubercle bacilli were found in the gastric washings. The biliary obstruction in these cases was presumably caused by enlarged portal glands.

Tuberculous meningitis has not been common in cases of congenital infection, possibly because early death has precluded the development of a Rich focus. Siegel (1934) found only three examples in 38 case reports. A more recent case in which the meninges were involved was recorded by Lesné, Cayla, Roche and Allard (1949).

The mother of this infant developed miliary tuberculosis and meningitis in June, 1948. She received a total of 60 g. of streptomycin in the four weeks preceding parturition. The placenta was examined for tuberculous lesions and acid-fast bacilli, but none were found. The infant weighed 2,360 g. at birth and appeared normal. When he was 5 weeks old streptomycin treatment was started because a radiograph of the chest 'montrait une image granulique'. Two weeks later (the infant being only 54 days old) increased tension was noticed in the anterior fontanelle and so lumbar puncture was performed. The cell count and protein content of the cerebrospinal fluid were increased but Koch's bacilli were not found on direct examination. Another specimen obtained later caused tuberculosis when inoculated into a guinea-pig. Treatment with streptomycin was continued for nine months after which the cerebrospinal fluid was normal. When 1 year old the child weighed 8 kg. and appeared well.

Diagnosis. Of what value are the usual aids to diagnosis when applied to tuberculous infection of congenital origin, and does the condition of the mother and examination of the placenta help in predicting the likelihood of the disease?

THE INFANT. Experience with B.C.G. vaccination has shown that the young infant is capable of producing a positive tuberculin skin reaction.

In many case reports of congenital tuberculosis the Mantoux reaction is not mentioned. In my patient it did not become positive until the infant was 7 months old in spite of the added stimulus of B.C.G. vaccination. A positive response to intradermal P.P.D. has, however, been found as early as the twenty-first day of life, and in this case (Amick *et al.*, 1950) it preceded all symptoms of illness. An intradermal tuberculin test may be helpful in diagnosis, but its value will be diminished by the increasing use of B.C.G. for newborn infants.

Siegel (1934), reviewing the pathological findings in 38 cases, found the lungs to be involved in 37 and

the liver in only 31. As lung infection is common and usually extensive, examination of the fasting stomach contents for tubercle bacilli is likely to give a positive result. This was so in my patient and in a number of others in the literature. It is probably the quickest and most helpful way to establish the diagnosis. The value of the chest radiograph needs no emphasis.

Confirmation of the diagnosis during life has been made by histological examination of material from an infected mastoid, a cervical lymph node and tibial bone marrow (Amick *et al.*, 1950).

THE MOTHER. In some reports of congenital tuberculosis the mother's lesion has been recorded as 'slight' or 'mildly active', and her progress has been good. More commonly she has had a severe generalized infection, and in more than half the reported cases has died within a few weeks of parturition. On the other hand, there are many records of women with severe miliary tuberculosis giving birth to healthy infants.

In five cases the mother has shown no evidence of tuberculosis at the time of delivery (Straus, 1895; Morley, 1929; Söderström, 1932; Pagel and Hall, 1946 and 1948; Hughesdon, 1946). In one (Pagel and Hall) the mother developed widespread and fatal tuberculosis 12 months later, but in Hughesdon's report she was still alive and apparently healthy two years later.

When the mother has tuberculosis of the pelvic organs the infant may aspirate infected material from the liquor amnii or the birth canal. Undoubted cases of transmission of the disease by this route are rare. In 1939 Reichle and Wheelock found only eight acceptable cases of this nature in the literature. In all of these the infant quickly succumbed to severe tuberculous bronchopneumonia.

To keep this problem in perspective it is good to recall Debré's study of 1,369 infants born to tuberculous mothers. None showed evidence of congenital infection over a period of four years (Rich, 1944).

THE PLACENTA. The foetus of a tuberculous woman escapes infection far more often than does the placenta. Schmorl and Geipel (1904) examined 20 placentae from tuberculous mothers and found microscopical lesions in nine, though the infants remained healthy. Pathologists engaged on routine hospital work will note with interest that these workers examined 2,000 sections from one case before demonstrating the disease. Inspection and microscopy of the placenta are not therefore of practical help in finding cases of congenital tuberculosis. In view of the frequency of placental infection, however, there is much to be said for the recommendation of McIntyre, Drimmie and Gordon (1953) that milking the cord and delay in its ligation should not be practised when the mother has tuberculosis.

Management. Congenital tuberculosis is rare and in the past has often proved rapidly fatal. The likelihood that it will occur in any particular case cannot be predicted by consideration of the mother's lesion, nor by the presence of foci in the placenta. All infants born to tuberculous mothers (whether 'active' or not) should therefore be kept under close observation, particularly during the first two months of life. If there is any departure from normal health, samples of the gastric content should be examined for tubercle bacilli by direct microscopy, as well as by culture and guinea-pig inoculation. Radiographs of the chest taken at the age of 2, 4, 6 and 8 weeks may also be helpful. There is no need to perform a Mantoux test before giving B.C.G. vaccination as was advocated by Mason (1954). This would cause unnecessary delay, for the vast majority of infants are not infected, and it might be negative in the presence of infection. The danger of provoking Koch's phenomenon by vaccinating an infant during the early stage of infection is probably very slight, if indeed it exists at all. This problem was fully discussed at the Conference on European B.C.G. Programmes and in its report Dr. H. J. Ustvedt (1951) writes 'there is very little evidence to indicate that tuberculous disease occurring in individuals vaccinated with B.C.G. in the pre-allergic phase is more serious than where no B.C.G. has been given'.

As soon as it is likely that an infant is infected, treatment with streptomycin and isoniazid should be started without delay and continued for six months. P.A.S. may cause severe digestive upsets in the newborn (Delthil, Péretti de la Rocca and Thévenier, 1952) and is probably unnecessary.

Summary

A case of congenital tuberculosis is recorded. The infant received B.C.G. vaccine before symptoms developed and responded to treatment with streptomycin and isoniazid. The symptomatology, diagnosis and treatment are discussed. Direct examination of the gastric contents for acid-fast bacilli is probably the most rapid way of confirming the diagnosis.

I wish to thank Dr. O. F. Thomas for giving me clinical details of the patient's mother.

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STUDIES IN A CASE OF 'RENAL RICKETS'

BY

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The syndrome of secondary hyperparathyroidism due to chronic renal insufficiency is well recognized. A full discussion of the mechanisms involved can be found in Albright and Reifenstein's book (1948). Briefly, the sequence of events is renal insufficiency, phosphorus retention, a low serum calcium level and resulting parathyroid hyperplasia with skeletal changes and frequently metastatic calcification.

The condition can occur in both acquired and congenital renal disease with both glomeruli and tubules, or tubules alone, affected. The skeletal changes associated with the Fanconi syndrome (1936) are an example of the latter, which is discussed by McCune, Mason and Clarke (1943) in their paper. In this type phosphate is not retained.

Hyperparathyroidism secondary to renal disease can occur at any age. As a rule the renal failure is of considerable duration. Some of the changes described by Ellis and Evans (1933) in a series of children seem due to this condition. The skeletal changes in children are described in detail by Gilmour (1947).

The following case is recorded, first, because unusually severe skeletal changes were the presenting features in an illness which investigation showed to be renal in origin, although symptoms of renal failure were initially minimal; secondly, the results of full investigation were available for study.

Case Report

The patient was a girl aged 16 years. She was referred to the neurological clinic in May, 1954, and admitted directly to the ward. She had complained of pain in both knee caps for one year. Her parents thought she had been rather pale for a longer period. In August, 1953, she was seen to be dragging the right leg towards the end of the day. By February, 1954, she had developed a knock-knee deformity of both legs. From then until she was admitted to hospital her walking had become steadily worse with a scissor type of gait. She complained of some breathlessness on exertion. She had no frequency, nocturia or other urinary symptom. Menstruation had begun at 14 years and was normal, 3/28 days. There was no known previous renal disease or streptococcal infection. Her mother and father were well. Her brother was fit, being an Army cadet at Sandhurst. One cousin was a mental defective and epileptic.

On examination the patient was small for her age and pale, but the secondary sex characters were well developed. A dorsal kyphoscoliosis was present, the radii and ulnae were bowed, the costochondral junctions were much enlarged visibly and palpably. The lower limbs showed severe genu valgum with slight pes cavus. The pulse was 120/min. regular. Blood pressure was 130/80 mm. Hg. The heart was not clinically enlarged. A systolic murmur was heard over the apex and pulmonary areas. There was no oedema. The respiratory system was normal. The liver, spleen and kidneys were not palpable. The central nervous system and fundi were normal; particularly no neurological signs were found in the lower limbs, where power and coordination were normal considering the bony deformity. No enlarged lymph node or other swelling was palpable in the neck.

Investigations on May 22 showed the urine to be pale and clear with a specific gravity of 1,010, an alkaline reaction and albumin, 2 g./l. In a centrifuged deposit, an occasional hyaline cast was found. The urine was sterile on culture and cloudy on the Sulkowitch test.

The urinary findings showed little variation during the patient's stay in hospital.

On May 23 the blood E.S.R. was 40 mm. in the first hour (Westergren), Hb 40% (Sahli), R.B.C. 1·94 m./c.mm., W.B.C. 4,100/c.mm. The Wassermann and Kahn reactions were negative. A film showed microcytic and hypochromic red blood cells and normal white blood cells.

Radiographs taken on May 26 showed that both kidneys were exceedingly small, with no definite renal calcification but calcification of pelvic vessels. The skeletal changes are shown in Figs. 1-5.

Because of the patient's poor general condition and renal function, neither intravenous nor retrograde pyelography was carried out.

The patient showed no change while she was in hospital. Daily urine examination showed the specific

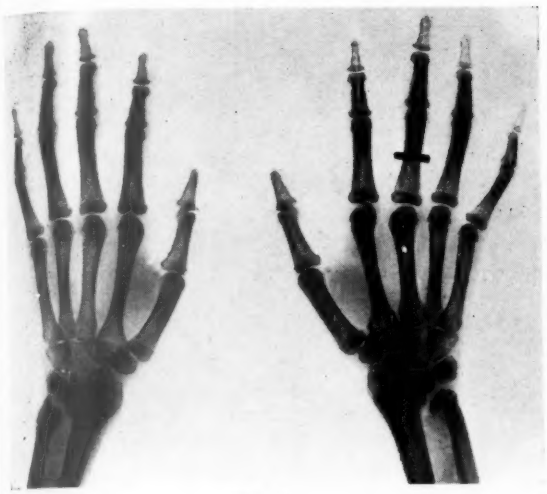

FIG. 1

FIG. 2

FIG. 3

ew bone formation was seen at all costochondral regions, d faintly calcified osteoid at the outer ends of the clavicles. he upper ends of the humeri showed demineralization and eformity with the 'rotting stump' appearance. There was bluxation of epiphyses at the wrists. There was lace-like eriosteal new bone formation in the hands, radii and ulnae. he skull showed pepper-pot demineralization. The legs owed genu valgum with changes in the metaphyses. The opliteal vessels were calcified.

FIG. 4

FIG. 5

gravity fixed at 1,010, reaction alkaline and 1·5-2 g./l. of albumin. There were never more than a few hyaline casts in a spun deposit. On June 10, 3 pints of blood were given, and the haemoglobin rose from 40% to 57%. The level after further transfusion on July 2 was 65%. She also received 600 mg. % of 'ferrivenin' in divided doses, but with little effect. From June 26 onwards she was given 30 grains pot. cit. four-hourly. On June 28 the CO_2-combining power had risen to 63 vol. %, but fell to 34 vol. % on June 30. The blood pressure varied from 150/100 to 130/80 mm./Hg. The E.S.R. varied from 95 to 40 mm. in the first hour. The patient went home on July 3.

Following an epistaxis she was readmitted on August 26. Her general condition had deteriorated. She was very ill, breathless at rest and pale, with oedema of the face. Haemoglobin was 25%, pulse 120 per minute, blood pressure 140/90 mm./Hg. On August 27 the urine was unchanged except that it contained 3 g./l. albumin. The reaction was alkaline (for biochemical findings see Table 1).

The patient was given 4 pints of blood and the haemoglobin rose to 70%. She returned home on August 28. She deteriorated steadily and died at home in November, 1954.

No necropsy was performed.

Discussion

This patient had severe hyperparathyroidism with gross skeletal deformity secondary to renal failure which was probably due to congenital hypoplasia of the kidneys and was the cause of death.

The renal lesion was relatively silent, the patient coming to hospital with difficulty in walking, and painful and deformed lower limbs. On investigation, the picture was in fact one of severe 'renal rickets', a renal osteitis fibrosa generalisata. Albright, Drake and Sulkowitch (1937) suggest that this condition resembles true rickets only in the radiological appearances. At the same time, they point out that epiphyseal changes are never seen in primary hyperparathyroidism without accompanying renal failure.

The radiological evidence for hyperparathyroidism in this case is extensive, e.g., the pepper-pot skull, the fine periosteal new bone formation and the arterial calcification in someone aged 16 years. (The teeth were not radiographed but in less obvious cases the absence of the lamina dura around them may be helpful (Strock, 1941).) These changes are superimposed on widespread faulty calcification of osteoid as seen in rickets.

The biochemical findings of normal low serum calcium, high serum inorganic phosphorus, high alkaline phosphatase plus the serum and urine calcium levels on a low calcium intake are in keeping with hyperparathyroidism.

That the renal failure was severe is shown by the low fixed specific gravity of the urine, the poor urea clearance, the raised serum phosphorus, creatinine and non-protein nitrogen, plus the low CO_2-combining power. A congenital cause for this is suggested by the absence of any acute episode in a child, and the paucity of uraemic symptoms in the face of such a degree of renal failure. The extremely small renal shadows also favour congenital hypoplasia.

It may be that a few years before coming to hospital the patient and her metabolism outgrew the functional capacity of the kidneys with ensuing renal failure and hyperparathyroidism. Severe renal damage may be the presenting feature in primary hyperparathyroidism, but the absence of

TABLE 1

BIOCHEMICAL FINDINGS

	24/5/54	27/5/54	28/5/54	29/5/54	30/5/54	31/5/54	2/6/54	4/6/54	6/6/54	9/6/54	10/6/54	28/6/54	30/6/54	2/7/54	27/8/54
Plasma albumin (g. %)	4·35							4·0				3·31			3·31
Plasma globulin (g. %)	2·6							2·63				2·26			2·9
N.P.N. (mg. %)	128							191				182			241
CO_2-combining power (vol.%)	39		36					29				63	34	48	23
Serum Ca (mg. %)	12·1		9·9		9·0	8·6	9·7	9·3	9·3		9·0				11·4
Serum Na (mg. %)			300												
Serum inorganic P (mg. %)	2·8		5·2		5·2		5·3	5·1			4·8				12·2
Serum K (mg. %)			165												
Cephalin cholesterol flocculation test	Neg.														Neg.
Serum creatinine (mg. %)		5						3·2							
Blood cholesterol (mg. %)		295						294							213
Urea clearance (mg. %)			58												
Urine volume (ml./24 hr.)				1,180					1,420	1,060					
Urine Ca (mg. %)				10·5					7·5	8·1					
Alkaline phosphatase (K-A units)	25						24	28							17

(From May 31 to June 9, 1954, on low Ca diet 0·16 g./24 hours.)

renal calcification along with the clinical, radiological and biochemical findings exclude the diagnosis in this patient.

Treatment in this case could only be symptomatic in view of the degree of renal failure. The anaemia of uraemia is notoriously resistant to treatment, and the only helpful measure here was transfusion, intravenous iron having no effect.

Alkali was given as 30 grains potassium citrate four times daily from June 26 until the patient left hospital. This was the maximum dose the patient could tolerate and it caused the CO_2-combining power to rise to 63 vol. % on June 28. However, the figure had fallen to 34 vol. % by June 30. This change presumably reflected variations in the remaining renal function as other factors were relatively constant. Alkali could hardly be expected to have a sustained effect here as the biochemical findings showed glomerular as well as tubular failure. In this condition the acidosis is due not only to loss of base following failure of ammonia synthesis as in pure tubular lesions, but also to accumulation of acid radicals. It is important to try and distinguish the two types of underlying renal lesion, as the prognosis is reasonably good in some pure tubular lesions if alkali and vitamin D are given. Massive doses of the latter have been suggested as a means of increasing calcium absorption from the gut, lessening the negative calcium balance and reversing the skeletal changes in hyperparathyroidism secondary to renal acidosis without glomerular insufficiency, the rationale being the lowered gastric acidity and poor calcium absorption in acidosis described by Browne and Vineberg in 1932. It would have been of little avail in the present case. The biochemical findings on her second visit to hospital showed severe uraemia from which she died some weeks later.

Summary

A case of 'renal rickets' due to probable congenital hypoplasia of the kidneys and secondary hyperparathyroidism is reported. The clinical, radiological and biochemical features are discussed in relation to diagnosis and treatment.

I wish to thank Dr. James K. Slater of Edinburgh Royal Infirmary for permission to publish this case, also the staff of the Radiological and Biochemical Departments for valuable cooperation.

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EXOMPHALOS

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Exomphalos is a rare condition in which there is a congenital malformation of the umbilical cord, alone or combined with a defect of the supra-umbilical region of the abdomen, and through which the viscera herniate into a sac covered by amniotic membrane and peritoneum. The sac may vary in size in its largest diameter to as much as 15 cm. and, according to size, will contain varying amounts of intestine, stomach and liver. The neck of the sac is surrounded by skin with a clear line of demarcation, and occasionally the skin extends a short way up the side of the sac. Exomphalos includes conditions described under the following names: omphalocoele, amniocoele, amniotic hernia and hernia into the umbilical cord.

Embryological Aspect

The condition at birth resembles the appearance in embryos before the tenth week of foetal life with the coelomic cavity as a forward extension into the base of the cord, the pocket containing intestine and other abdominal viscera. Normally, after the tenth week, the organs are withdrawn into the abdominal cavity. There have been a number of theories in regard to aetiology:

(1) It is due to retardation in the development of the abdominal cavity about the third month of foetal life, causing the abdominal organs to remain in the cord pocket because of insufficient room in the abdomen.

(2) It is due to a disparity between the size of the abdominal cavity and the viscera, which has resulted from retarded development of the abdominal parietes.

(3) The following theory is put forward by Margulies (1945), after study of the work of Pernkopf (1925), Politzer and Sternberg (1930), who each studied the formation of the anterior abdominal wall of human embryos in the early weeks of pregnancy. According to Margulies the combined umbilical and supra-umbilical defect follows a failure of development about the third week of embryo life, whereas a purely umbilical ring defect originates at the eighth to tenth week. In the latter case there is a normal anatomy of the upper abdominal aponeurosis. The supra-umbilical defect is due either to failure of the amniotic covering to become closely adherent to the transverse septum, or failure of the connective tissue of the transverse septum to proliferate and thus to push the umbilical covering downwards towards the umbilical pedicle. An umbilical ring defect could be caused by failure in the proliferation of the adventitial connective tissue of the umbilical vessels.

Those who accept Margulies' view differentiate hernia into the umbilical cord from the combined umbilical and supra-umbilical defect, which they classify as 'omphalocoele'. In hernia into the umbilical cord there is generally only intestine outside the umbilical ring, the neck of the defect having a diameter of about 4 cm. or less, the sac when unruptured being covered by peritoneum and amniotic membrane. In omphalocoele the sac is also covered by peritoneum and amniotic membrane, but the neck of the sac is generally larger than 4 cm. in diameter, and the sac may contain not only small and large intestine, but other organs such as stomach and liver, thus presenting a much more difficult problem in treatment. Although there may be justification at times in separating the conditions from the embryological concept, it is simplest in reviewing the literature to retain the inclusive term 'exomphalos'.

The Literature

An extensive review by Jarcho (1937), covering about 450 cases, did not show any hereditary tendency. On the other hand in a short series of seven cases, Benson, Penberthy and Hill (1949) included a brother and sister, each showing a hernia into the umbilical cord. Paucot and Gellé (1936) described a similar condition in three successive pregnancies in a young woman.

Associated congenital abnormalities occur with more than coincidental frequency. In Ladd and

Gross's series of 88 cases 59% had some other abnormality (Ladd and Gross, 1941), in most cases of minor degree. Twenty-eight per cent. had malrotation of the intestine with intestinal obstruction, requiring operation at the time of repair or subsequently.

Since the latter half of the nineteenth century various efforts have been made to treat the condition surgically. A review of the literature, however, gives a biased impression, and one must assume that with large examples of exomphalos there has been a tendency to report only the successful or near-successful results. Earliest successes were in cases which we would now classify as 'hernia into the umbilical cord'. The earliest was published by Visick in 1873. Aribat (1901) and Walravens (1902) between them collected about 200 cases up to 1900. Altpeter (1931) collected 109 cases between 1900 and 1929, adding three of his own. Jarcho (1937) collected 46 cases between 1929 and 1937, adding one of his own. Of these 47 cases, 36 were submitted to radical surgical operations, and in these there were only five deaths. Massabuau and Guibal (1933) collected 23 cases, mostly from the European literature and added one of their own. Operations had been performed in 12 cases where the abdominal defect was 4 cm. or less in diameter, and there were nine recoveries. Jarcho, in his analysis, reported that of 159 cases since 1900 the liver was in the sac in 46 cases, and of these 12 recovered after operation, giving a recovery rate of about 25%.

A truer picture, however, is given by Gross (1953), who states that in patients treated in a series from 1940 to 1950 inclusive, the mortality rate was 34% for those accepted for surgery. Of the 20 deaths in the series, four were due to congenital heart disease, and one to an infected meningocoele. In six of the children who survived there was a subsequent operation for the treatment of intestinal obstruction due to malrotation of the intestine.

Many of the deaths in the early cases were due to injudicious crowding of the viscera into the abdomen

TABLE
RECOVERY WITH SURGICAL TREATMENT

Weight	Diameter of Abdominal Defect (cm.)	Contents of Sac	Age at Operation (hr.)	Type of Operation	Result	Author
7 lb. (3,175 g.)	11·25 × 6·25	Whole liver, most of intestine	12	Sac excised, one-stage closure	Ventral hernia	Hipsley (1929)
7½ lb. (3,402 g.)	Hernia 'size of child's head'	Entire liver, two-thirds stomach, pancreas and most of intestine	—	Sac excised, one-stage closure	Good result	Dott (1932)
6 lb. 14 oz. (3,118 g.)	—	Whole liver	12	One-stage closure	Strong scar when 3 years old	Jarcho (1937)
6 lb. 10 oz. (3,005 g.)	7	Liver, stomach, small intestine	8	First-stage closure	Second-stage operation 22 mth., good result	Benson *et al.* (1949)
—	Size of tennis ball	Larger part liver, large and small intestine	36	One-stage repair	Ventral hernia followed with more or less spontaneous cure by 1954	Nash (1950). (Surgeon, C. Donald. Subsequent report, H. H. Nixon)
Full term	10	Liver, small intestine..	48 approximately	Sac excised, attempt at one-stage repair	Resuture of wound 8 days after first operation and 8 days after second. Awaiting repair of two incisional hernias	
Full term	11	Almost entire liver, part of small intestine	10	Sac excised, diaphragmatic hernia present, skin closure only	Recovery from first operation. Two subsequent attempts at repair, but large ventral hernia still present at 3 yr.	Fox (1951)
5 lb. 8 oz. (2,495 g.)	10	Most of liver, spleen and large and small intestine	58	Sac not opened, first-stage closure with difficulty	Skin flap necrosed 6 days after operation and treated by skin graft. Second repair operation due at 14 months	Welch (1951)

in a one-stage operation, which caused heart failure due to pressure on the inferior vena cava by the forcibly replaced liver. Gross, in 1948, advised not opening the amniotic sac at the first operation, but instead freeing, undercutting and approximating the skin margins over the sac, thus preventing adhesion of the abdominal viscera to the subcutaneous tissue. A second-stage repair operation could be delayed until the child was 6 to 12 months of age. Other surgeons, however, while accepting the advance of the two-stage operation, have remained of the opinion that the sac should be opened at the initial operation, because of the danger of associated intra-abdominal congenital malformations.

The Table lists certain cases, in which the exomphalos was relatively large, and are some of the best examples of recovery with surgical treatment.

I have been privileged to see some notes and photographs of a patient treated in The Hospital for Sick Children, Great Ormond Street, London, by D. L. B. Farley (1955), who operated on a baby boy under the care of G. H. MacNab in 1953. There was a large exomphalos containing the liver and most of the intestine, with measurements at the base 6 cm. by 5 cm. The sac was removed at the first operation, and a one-stage repair attempted. The wound broke down, and as closure was impossible, a large patch of amnion was sewn in place overlapping the defect approximately one inch all round. The skin again broke down, but the amnion remained intact, preventing evisceration. The wound was re-sutured, and the child recovered. In November, 1955, he was reported as fit and well, but with an enormous ventral hernia, and with the lower ribs growing inwards, tending to bisect the liver.

Before 1940 rupture of the sac before operation was mostly fatal, but since then the advent of chemotherapy and the wide selection of antibiotics have improved the outlook. If the rupture has taken place after birth, the prognosis is better than where it has occurred during intra-uterine life and the intestines have become oedematous and matted together.

Conservative Treatment

Only brief mention of this is to be found in the literature. One of the early methods of treatment was to apply a protective bandage, without any attempt to reduce the hernia. Aribat (1901) lists some cases of this type. In 1899 Ahlfeld described a method whereby the hernia was reduced as far as possible under light narcosis after careful cleansing of the sac and surrounding skin, followed by alcohol compresses. In the first case he treated the liver was in the sac, and complete reduction was impossible, but the child thrived without operation, and one year later the scar was excised and the wound closed. In Jarcho's review of 46 cases, reported between 1929 and 1937, there was one recovery with Ahlfeld's method, but the child was accidentally killed at the age of 7 months. Ahlfeld's method, however, never found favour. Gross (1953) stated that in one of their personal cases the skin of the abdominal wall had started to grow up over the margins of the sac, and they were encouraged to think this would continue, so operation was deferred, but unfortunately infection set in and the infant died. Ellison Nash (1950) reported a case of an exomphalos the size of a large orange at birth. Cure was spontaneous, leaving an umbilical hernia with a ring 2·5 cm. in diameter. The dimensions of the neck of the sac were not given. Nash recommended a dressing of penicillin and sulphonamide cream. Denis Browne (1955) has successfully treated two cases of the hernia into the cord type by simply twisting the cord so as to squeeze the contents back into the abdomen, and then strapping down as for an umbilical hernia.

In view of the poor results experienced in the surgical treatment of cases of large exomphalos, it was decided in 1948, without knowledge of Ahlfeld's work, to try conservative treatment using absolute alcohol dressings in conjunction with an antibiotic, penicillin. Two cases were treated with results as follows:

Case Reports

Case 1. R.H., a boy, was born normally on December 5, 1948 (weight 5 lb. 10 oz. 2,551 g.). Exomphalos with unruptured sac contained intestine, stomach and part of the liver. The sac was 6 cm. in diameter at the neck. Absolute alcohol dressings were applied twice daily.

December 6. Feeding begun. Bowels opened normally.

December 9. Feeds taken well. No vomiting. Amniotic sac discoloured and becoming black.

December 15. Sac moist, black and necrotic in appearance. Swabs showed non-haemolytic streptococci only. Penicillin treatment begun, 30,000 units, four hourly, by injection.

December 23. Feeding satisfactory. No vomiting. Exomphalos area shrinking. Less discharge on dressings. Baby's weight 5 lb. 11 oz. (2,580 g.).

December 29. Sac wall hard, dry and black. Small area of moist granulation tissue at the edge. Haemoglobin 90%.

December 30. Progress maintained. Swab from exomphalos showed *Staphylococcus aureus* sensitive to penicillin. Penicillin injections discontinued, but penicillin continued by mouth.

FIG. 1.—R.H. in August, 1954, in the recumbent position, head raised.

FIG. 2.—R.H. in April, 1955, after operation on March 16, 1955.

January 4, 1949. The granulating area uncovered by skin had contracted to 5 cm. in diameter.

January 7. Feeding satisfactory. Penicillin discontinued.

January 11. Exomphalos area more moist. Penicillin again started by mouth. Alcohol discontinued. Eusol dressings applied. Weight 7 lb. (3,175 g.).

January 23. Feeding satisfactory. No vomiting. Stools normal. Exomphalos area still moist in the centre. Penicillin continued by mouth.

February 4. General progress satisfactory. The granulating area of the exomphalos had contracted to about 1 cm. in diameter. Eusol dressings discontinued. Scarlet red ointment applied. Weight 8 lb. 4 oz. (3,742 g.).

February 13. Exomphalos healed. Left inguinal hernia noted for the first time. Penicillin discontinued. The child was discharged from hospital, 70 days after birth. Weight 9 lb. (4,082 g.).

FOLLOW-UP. The baby was seen again on May 30 when he was 6 months old. Weight 15 lb. (6,804 g.). Normal development. There was an abdominal herniation 5 cm. wide, 6½ cm. long, with puckered skin 2 cm. in diameter in the central area. A large left inguinal hernia present.

July 13. Developed ischio-rectal abscess. Treated surgically. Quick recovery. Bilateral inguinal hernias noted, left much larger than the right.

On January 22, 1950, when the child was 1½ years old, recurrent vomiting was reported. Inguinal hernias present. The child had stood up for the first time at between 10 and 11 months of age, and was walking quite well when seen. He started to talk soon after 1 year of age.

On January 28 he was admitted for left inguinal herniotomy.

On April 13, 1951, he was admitted with complaint of attacks of abdominal pain with screaming and occasional vomiting. The child settled quickly in hospital. Radiological investigation was negative.

On November 30, 1953, the child weighed 37 lb. (16·4 kg.), was very well apart from a central abdominal defect with herniation, extending from the xiphisternum to the umbilicus. The bulge on standing was 5 cm. by 9 cm.

On October 13, 1954, the mother again gave a history of intermittent abdominal pain with some abdominal distension. The herniation on standing was 7·5 cm. by 10 cm.

On March 5, 1955, the child was admitted with the history of frequent attacks of abdominal pain and vomiting. Radiological examination was again negative. It was decided to repair the abdominal hernia defect.

On March 16 operation was performed by Mr. R. H. Franklin. A transverse incision was made and the puckered area in the middle of the scar was excised. The peritoneum was opened showing numerous adhesions between coils of intestine. Several adhesions were divided. The appendix was removed. The hernia was closed with a Mayo type repair using catgut. The child made an uneventful recovery after operation, which produced a very satisfactory cosmetic result (Fig. 2).

On May 2, there was again a history of recurrent abdominal pain and occasional vomiting, but conservative measures were adopted. The symptoms were probably due to adhesions.

Case 2. S.C., a boy, was born on November 15, 1949. Birth weight was 6 lb. 15 oz. (3,147 g.). A large exomphalos was present, the sac unruptured, 8 cm. at the neck (Fig. 3). It contained liver, stomach and the greater part of the intestines. Absolute alcohol dressings were applied twice daily. Penicillin, 60,000 units three hourly by mouth, was given.

November 18. The child's condition had deteriorated considerably since birth. He was very ill with poor colour and rapid respirations and intermittent vomiting. There were signs of dehydration. Penicillin was changed to the intramuscular route, and 100 ml. of 4·3% glucose in 1/5 normal saline given intramuscularly.

November 19. Vomiting frequently, coffee ground in type. Well marked dehydration, and 150 ml. normal saline given intravenously followed by slow drip using 4·3% glucose in 1/5 normal saline.

November 21. Condition remained very poor.

Vomiting less marked. One large stool with excess mucus. Feeding by pipette and oesophageal tube, using expressed breast milk in small quantities, retained.

November 22. Very weak—grey. Generally about one large vomit in 24 hours. Intravenous drip changed to intramuscular drip.

November 23. Still extremely ill. Vomited twice in the previous 24 hours. The abdomen was distended, but the motions were normal in appearance. Intramuscular fluid therapy continued.

November 24. Abdomen distended. The exomphalos area was black and gangrenous in appearance with offensive discharge. Absolute alcohol dressings continued.

November 25. There was slight improvement. The vomiting continued, but small feeds up to 6 drachms E.B.M. every one-and-a-half hours were for the most part retained. Penicillin continued. Absolute alcohol dressings continued.

November 28. The abdomen became more distended. The respiration rate was raised, and there were recurrent attacks of cyanosis. The exomphalos area was moist with offensive discharge, increasing in amount, but the skin was growing in satisfactorily from the edge. Absolute alcohol dressings alternated with 'eusol' dressings.

November 29. The child was weak and dehydrated. Respirations rapid and distressed. Abdomen distended. Vomiting more frequently. Stools normal. The child responded to intramuscular fluid therapy. Weight 6 lb. 2 oz. (2,778 g.).

December 1. Improved. Temperature still raised to 100° F. Intramuscular drip continued.

December 3. Temperature raised. General condition improved. There was an offensive discharge from the exomphalos area. By this time the child was taking breast milk, 1½ oz. two hourly by bottle, without vomiting.

December 6. Temperature between 100° F. and 102° F. Vomiting had begun again, so feeds were reduced in amount. Motions normal. Weight 6 lb. 6 oz. (2,892 g.).

December 8. Temperature normal. Small feeds retained well. General condition improved.

December 10. Covering of the exomphalos area thick and greenish-black with a raw area 8 cm. in diameter. The skin was growing in at the edge, and the lateral bulging of the swelling was less marked.

December 12. Vomiting re-started with rapid respirations and recurrent cyanotic attacks, probably following an aspirated vomit. Intramuscular saline again given.

December 13. Vomiting in small amounts continued. Intramuscular glucose saline continued. Weight 6 lb. 7 oz. (2,920 g.).

December 18. Slight improvement. Expressed breast milk taken, 1½ oz., two hourly.

December 22. General condition improved, but occasional vomiting interrupted progress. The surface of the exomphalos still had a black area of necrosis, but skin edges were cleaner in appearance, and about 7½ cm. apart. The tumour swelling was 6½ cm. above the general level of the abdomen, and the widest diameter was 8 cm.

December 24. The child was taking 2½ oz. National

FIG. 3.—ABOVE.—S.C. at birth, anterior view of exomphalos. Widest diameters of skin defect, 8 cm. × 8 cm., and of exomphalos, 10 cm. × 10 cm.

BELOW.—Lateral view. Height of exomphalos above abdominal wall 4 cm.

FIG. 4.—S.C. on January 11, 1950, aged 57 days.

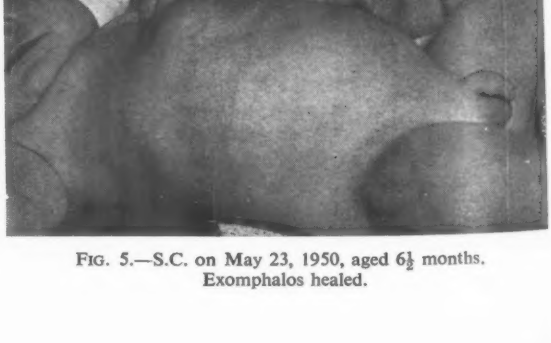

FIG. 5.—S.C. on May 23, 1950, aged 6½ months. Exomphalos healed.

dried milk three hourly. No vomiting. Absolute alcohol and 'eusol' dressings continued alternately.

December 29. Good progress maintained. The child reported as seeming hungry for the first time. The skin healing continued, and the discharge from the exomphalos was less offensive.

January 1, 1950. Penicillin, which had been given continuously from birth, was discontinued. Haemoglobin 68%.

January 13. Weight 8 lb. 1 oz. (3,657 g.). The raw exomphalos area was reduced to 5½ cm. in diameter.

January 24. Blood transfusion, 50 ml. of fresh blood given.

February 2. Good progress maintained. The raw area had decreased to between 4 cm. and 5 cm. in diameter. Scarlet red ointment only applied.

February 7. Area of granulation tissue had contracted to a circle about 2½ cm. in diameter. Weight 9 lb. 8 oz. (4,309 g.).

February 28. Again recurrence of vomiting, but without abdominal distension. There were several septic skin spots. Penicillin again given intramuscularly, 30,000 units four hourly.

March 3. Vomiting had ceased when the sepsis was brought under control. The raw area was contracting quickly.

March 5. Penicillin discontinued.

March 23. Exomphalos almost healed. There was an area of unhealthy central scar tissue with puckered skin, which would break down intermittently, producing a raw area with serous discharge, which would then crust and break down again.

On March 6 the patient was discharged from hospital (weight 12 lb. 8 oz., 5,670 g.) after a period of treatment extending over 143 days.

He was followed up as an out-patient. On March 25 there was still a small, unhealthy crust less than 1 cm. in diameter in the central part of the exomphalos area. The child's general condition was very good.

By June 20 the wound had closed completely. There was, however, a considerable central abdominal herniation with a muscle gap of about 8 cm.

By August, 1950, good progress was maintained, and development was generally normal. A belt was ordered to control the large abdominal herniation.

By October 10 the baby could sit up well, and was beginning to crawl. The mother herself, with considerable ingenuity, had made a binder which was much more satisfactory than the official truss provided.

When seen on January 9, 1951, the child was beginning to speak. He could crawl well. The muscle gap was well controlled by the home-made belt, although the central herniation scar was delicate and tissue-like in consistency.

When he was 16½ months old, on April 3, he had been walking for one month. The mother's only complaint was of occasional constipation requiring medicine from time to time.

When seen on November 13 the child was very well. He had a large herniation extending from the ensiform cartilage to the umbilicus with wide divarication of the recti.

FIG. 6.—S.C. on November 19, 1953, in the recumbent position, head raised.

His weight on September 3, 1952, was 29 lb. (13·1 kg.) and height 89 cm. His general progress was good, and he was reported to be of above average intelligence. The abdominal defect was less noticeable, and the skin over the exomphalos more healthy in appearance.

On November 3, 1953 (weight 32 lb., 14·5 kg.; height 98 cm.), he had a central abdominal defect 7·5 cm. by 15 cm. when lying down and 6·25 cm. by 11 cm. when standing. There was also considerable foreshortening of the sternum. Generally, however, there was good posture apart from slight valgus knee deformity.

On January 25, 1955, when 5 yr. 3 mth. (weight 37 lb., 16·4 kg.; height 113 cm.), the child's general health was good apart from attacks of vomiting brought on by articles of diet which he disliked. There was little complaint of abdominal pain. His general progress at school was very good, and he was rarely absent.

On examination there was a herniation defect when standing 7·5 cm. by 9 cm.; when lying flat with the head raised 12·5 cm. by 6·5 cm.; but when lying quietly at ease only a slight bulge 6·5 cm. vertically was noticed. There was a small central, puckered scar 4 cm. in diameter. There was little disability, so it was decided to defer any question of a repair operation until a later date.

Discussion

There is a general statement to the effect that exomphalos occurs about once in every 5,000 births. The figures for three large maternity units in this area are of interest:

Unit 1	Yearly number of live deliveries approximately	2,000
	Births over five years	10,000
	Exomphalos	small 2, large 1
Unit 2	Yearly number of live deliveries approximately	1,500
	Births over five years	7,500
	Exomphalos	small 1, large 2
Unit 3	Yearly number of live deliveries approximately	1,300
	Total over five years	6,500
	Exomphalos	small 1

TABLE 3
DEATHS FROM CONGENITAL EXOMPHALOS IN 1951 AND 1952

	Sex	1 Week	Under 30 min	Over 30 min. and under One Hour	Over One Hour and under One Day	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days
Mention of other congenital malformations	M	3	1	—	—	—	2	—	—	—	—	—
	F	2	—	1	1	—	—	—	—	—	—	—
No other congenital malformations	M	12	1	—	3	3	3	—	—	1	—	1
	F	11	1	—	2	3	2	1	—	1	—	1
Mention of operation	M	2	—	—	—	—	2	—	—	—	—	—
	F	2	—	—	—	—	1	—	—	1	—	—
No operation	M	13	2	—	3	3	3	—	—	1	—	1
	F	11	1	1	3	3	1	1	—	—	—	1
Total, 1951	M	15	2	—	3	3	5	—	—	1	—	1
	F	13	1	1	3	3	2	1	—	1	—	1
Mention of other congenital malformation	M	7	1	—	3	1	1	1	—	—	—	—
	F	2	—	—	1	—	—	1	—	—	—	—
No other congenital malformations	M	12	1	3	1	4	1	—	2	—	—	—
	F	9	1	—	3	3	1	—	—	—	—	1
Mention of operation	M	3	—	—	1	2	—	—	—	—	—	—
	F	5	—	—	1	2	—	1	—	—	—	1
No operation	M	16	2	3	3	3	2	1	2	—	—	—
	F	6	1	—	3	1	1	—	—	—	—	—
Total, 1952	M	19	2	3	4	5	2	1	2	—	—	—
	F	11	1	—	4	3	1	1	—	—	—	1

Thus out of a total of 24,000 deliveries there were in all seven exomphalos cases, of which three were large. It is interesting to note, however, that in this hospital, where we have on the average 1,500 deliveries a year, we have not had a child with a large exomphalos since November, 1949.

If we take statistics for England and Wales according to the birth rate, the figures for live births would be as follows:

1951 607,529
1952 673,735

Working on an average incidence of 1/5,000 births, this would give a total figure of approximately 120 cases a year, of which the majority would be small and easily treated surgically.

Thanks to the cooperation of the Registrar General, who supplied me with details of deaths from congenital exomphalos in the years 1951 and 1952, we have the figures in Table 3. In some, other congenital abnormalities were mentioned in association. In 1951 there were 28 deaths and in 1952 30 deaths. If we accept the figure of 120 cases a year as an average, this would mean that a quarter of the cases died each year. It is very probable that these deaths occurred mostly in exomphalos cases with large sacs, and from the statistics it would appear that operations were only attempted in a small proportion of the fatal cases. In 1951, for example, there was mention of operation in only four out of 28 cases, and in 1952 in eight out of 30 cases. The others apparently died without treatment, unless of course the mention of operation was omitted from the death certificate. All deaths occurred within one week of birth.

Summary

The literature on the treatment of exomphalos is reviewed.

Two cases of exomphalos with large, unruptured sacs treated conservatively with quite successful results are reported, proving that conservative treatment is worthy of trial. Alcohol and 'eusol' dressings were applied and penicillin administered by mouth and by injection.

I wish to acknowledge the valuable help of my assistants, Dr. E. G. A. Crawshaw and Dr. Vivian Usborne, Sister E. Hall and Sister J. V. Cooper, and the various members of the nursing staff who were responsible for the detailed treatment of the babies. I wish also to thank the Librarian at the Royal Society of Medicine for help with references, and also my secretary, Miss J. Osmond, for assistance in the preparation of this article.

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PAEDIATRIC SOCIETIES IN THE BRITISH ISLES

The following is a list of paediatric societies and their principal officers at the time of compilation. Alterations when they occur, information on new societies or any omissions from this should be passed to the Secretary of the British Paediatric Association.

I: National

British Paediatric Association
President: Professor F. M. B. Allen
Secretary: Dr. P. R. Evans
Institute of Child Health,
The Hospital for Sick Children,
Great Ormond Street,
London, W.C.1.

The Royal Society of Medicine, Section of Paediatrics
President: Dr. J. Vernon Braithwaite
Secretary: Dr. C. W. Kesson
Dr. Leslie Scott
The Royal Society of Medicine,
1 Wimpole Street,
London, W.1.

The British Association of Paediatric Surgeons
President: Denis Browne, Esq., F.R.C.S.
Secretary: D. J. Waterston, Esq., F.R.C.S.
The Hospital for Sick Children,
Great Ormond Street,
London, W.C.1.

The Scottish Paediatric Society
President: Professor S. Graham
Secretary: Dr. J. H. Hutchison
Royal Hospital for Sick Children,
Yorkhill,
Glasgow, C.3.

Scottish Surgical Paediatric Club
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Royal Hospital for Sick Children,
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19 Adelaide Park,
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Irish Paediatric Association
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Secretary: Dr. Sheamus Dundon
9 Fitzwilliam Place,
Dublin.

Welsh Paediatric Club
Secretary: c/o Professor A. G. Watkins
Department of Child Health,
Llandough Hospital,
Penarth,
Glam.

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Secretary: Dr. Norman S. Clark
374 Great Western Road,
Aberdeen.

Caernarvonshire and Anglesey Paediatric Club
President: Dr. R. Garym Thomas
Secretary: Dr. M. Slater
2 Brynteg Terrace,
Bangor,
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Kent Paediatric and Child Health Society
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12 Montpelier Row,
Blackheath, S.E.3.
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Manchester Paediatric Club
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St. Mary's Hospital,
Whitworth Park,
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Children's Hospital,
Ladywood Road,
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Sheffield Regional Paediatric Society
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Secretary: Dr. R. R. Gordon
58 Nether Edge Road,
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South West Regional Paediatric Club
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Secretary: Dr. J. Apley
Department of Child Health,
Children's Hospital,
St. Michael's Hill,
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Department of Child Health,
Alder Hey Hospital,
Liverpool, 12.

S.E. Metropolitan Regional Paediatric Society
Chairman: Dr. R. C. MacKeith
Secretary: Dr. S. D. V. Weller
50 Southborough Road,
Bickley, Kent.